Reprints of Medical Report on Minamata Disease

By

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MINAMATA DISEASE

Chronology and Medical Report

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...F MINAMATA

Chronology

1907	Jun Noguchi, founder of a company that later becomes the Chisso Corporation, builds a factory in Minamata.
1925	Chisso's first indemnity payments to fishermen.
1932	Chisso begins production of acetaldehyde.
1950	Fish begin to float in Minamata Bay.
1952	Boom days of Minamata begin. Population climbs toward 50,000. Cat "suicides" begin. Acetaldehyde production begins turning upward.
April 1956	First recognized case of Minamata Disease enters Chisso's factory hospital.
May 1956	Dr. Hosokawa reports the outbreak to the Minamata Public Health Department.
Summer 1956	Outbreak reaches "epidemic" proportions. Fear of contagious disease spreads. Discovery that some persons had been ill since 1953.
August 1956	Kumamoto University Research Group established to investigate the cause of the sickness.
Oct. 4 1956	Research Group reports that the sickness is a heavy-metal poisoning caused by eating the fish and shellfish of Minamata Bay. Warning issued that eating fish is dangerous.
1957	Search for the specific poison continues. Many theories developed. At this point fifty-two patients have been discovered, of whom twenty-one have died.
1958	Kumamoto Prefecture imposes a ban on selling (but not catching) Minamata fish.
Sept. 1958	Chisso diverts its acetaldehyde waste water to the Minamata River, ignoring Dr. Hosokawa's warning not to do so. A few months later sickness appears in the river area.
July 1959	Some Kumamoto University researchers report that mercury is the cause.
Oct. 7 1959	Dr. Hosokawa's cat #400 falls ill with symptoms of Minamata Disease.
Oct. 17 1959	Fishermen demonstrate; invade Chisso factory.
Nov. 1959	Dr. Hosokawa told by Chisso to discontinue experiments.
Dec. 1959	Cyclator installed.
Dec. 30 1959	*Mimai* contract signed between "old" Minamata patients and Chisso.
1962	Methyl-mercury chloride extracted from Chisso's acetaldehyde sludge. Cause and source proven beyond doubt.

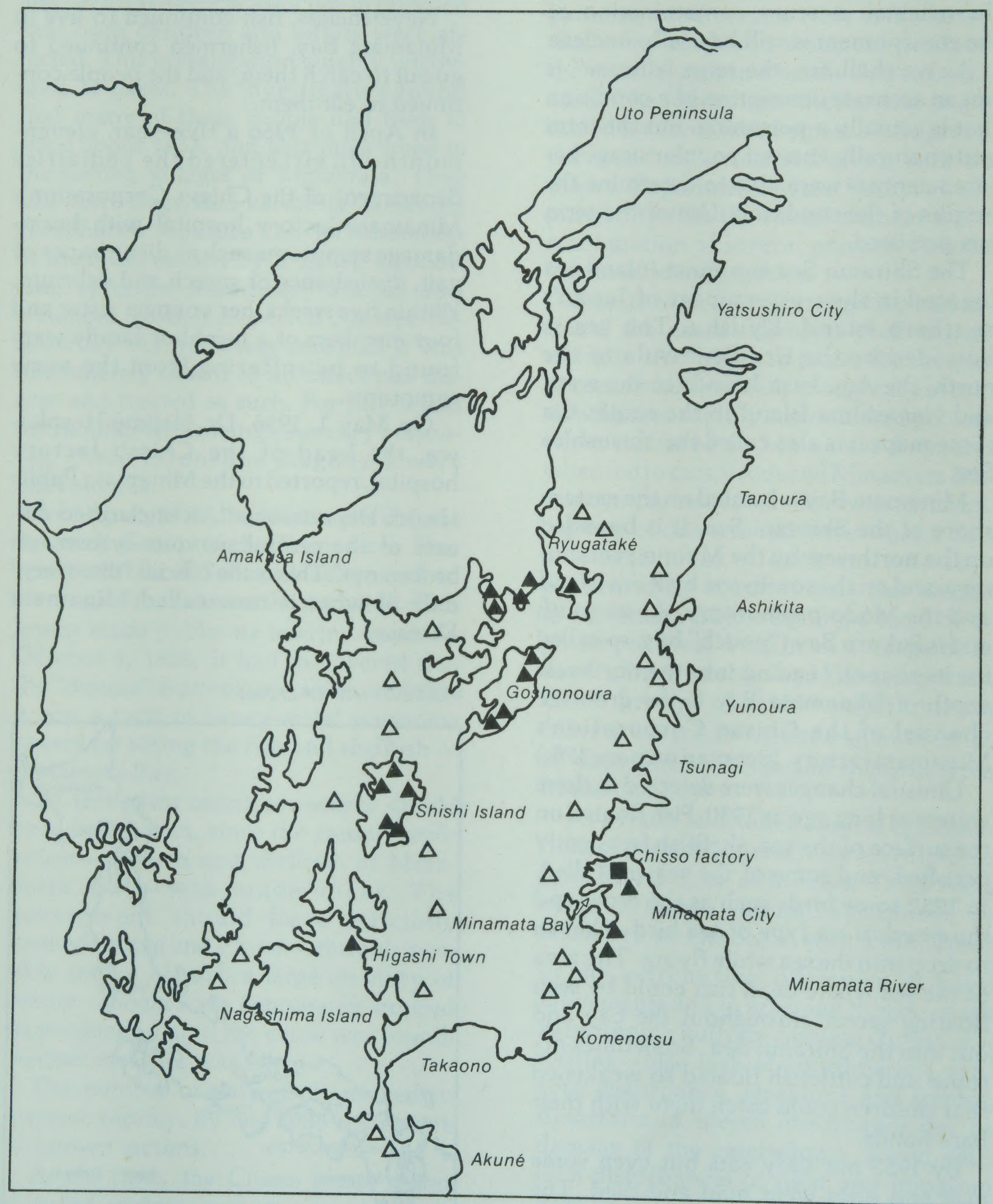
	People begin to eat the fish of Minamata Bay again. Minamata Disease considered "over." Verifications stop. 121 victims now verified, of whom forty-six have died.
1965	Niigata-Minamata Disease outbreak.
June 12 1967	Niigata-Minamata Disease patients sue Showa Denko.
Sept. 26 1968	Government announces its official stand that Chisso is the cause of Minamata Disease.
April 5 1969	"Old" patients split into two groups soon to be known as "leave it up to the other people" group and "trial" group.
	"Leave it up to the other people" group decides to ask the government to handle decisions on indemnity.
July 14 1969	Twenty-nine families (the "trial" group) file a lawsuit against Chisso.
1970	Kawamoto widens his search for patients.
May 1970	Ontario government announces that fish in Canada's English-Wabigoon River contain mercury. "Fish for Fun" signs appear.
May 25 1970	"Leave it up to the other people" group signs its settlement.
July 4 1970	Dr. Hosokawa testifies from his deathbed.
Nov. 1970	Central Pollution Board is established by Japanese government.
Feb. 19 1971	Eiichi Nishida, former head of the Minamata Factory, begins a year on the witness stand.
April 1971	Verifications of "new" Minamata patients begin.
Sept. 29 1971	Niigata verdict: plaintiffs win.
Oct. 6 1971	More "new" verifications. Eighteen patients form the "direct negotiations" group. All others decide to settle through the Central Pollution Board and become part of the "leave it up to the other people" group.
Nov. 13 1971	President Kenichi Shimada of Chisso comes to Minamata and signs a paper accepting moral (but not legal) responsibility.
Dec. 1971	"Direct negotiations" group begins sit-in outside Tokyo offices of Chisso. Lockouts and sieges result.
Jan. 7 1972	The Goi incident.
Jan. 11 1972	Iron bars installed at entrance of Chisso's Tokyo offices.
June 1972	Shinobu Sakamoto and Tsuginori Hamamoto attend the U.N. Environmental Conference in Stockholm, Sweden.
July 1972	Trial testimony taken in Minamata.
Oct. 14 1972	Last trial session. Verdict scheduled for early 1973.

Jan. 1973	Chisso has paid a million dollars so far in indemnities related to Minamata Disease.
Jan. 10 1973	Central Pollution Board "forgery" issue.
March 20 1973	Minamata Disease trial verdict: plaintiffs win. Chisso pays $3.2 million immediately.
March 22 1973	After-trial negotiations begin.
April 1 1973	Newly verified patient Kimito Iwamoto slashes at wrist. President Shimada says Chisso will pay $60,000 indemnity to Iwamoto, thereby setting a precedent for all other newly verified patients.
April 27 1973	Central Pollution Board announces its decision: $68,000 for heavy cases, $60,000 for lighter cases.
May 1973	Kumamoto governor declares that all fish outside of Minamata Bay, now marked by buoys, are safe.
July 9 1973	After-trial negotiations concluded. Settlement signed with Chisso.
1974	Number of verifications increases. Discovery of a patient who had fallen ill in 1943.
Jan. 1975	798 patients verified to date; 2800 applicants are still waiting. Chisso is paying all medical expenses, plus monthly allowances of $60.00 to $180.00 per patient depending upon degree of illness. Chisso has now paid indemnities totaling more than eighty million dollars. Project to dredge and fill in parts of Minamata Bay scheduled to begin.

MINAMATA DISEASE: A Medical Report

by Masazumi Harada, M.D., associated professor of constitutional neuropsychiatry, Kumamoto University, Japan, with Ailleen M. Smith, 180–192p., Holt. Rinehart and Winston. INC. New York, 1975.

FIGURE 1 MAP OF THE SHIRANUI SEA AREA



▲ Where Minamata Disease cats were discovered

△ Where fish were found floating

Minamata Disease is the first occurrence of widespread methyl-mercury poisoning caused by man-made environmental pollution that the world has experienced.

Minamata Disease was discovered in 1956 and its cause proved by 1959. Nevertheless, the present situation of the 100,000 persons who live within reach of the original mercury contamination of the environment is still basically unclear.

As we shall see, the term "disease" is not an accurate description of a condition that is actually a poisoning, but the term quite naturally entered popular usage before scientists were able to determine the origins of the condition. Use of the term has persisted.

The Shiranui Sea is a quiet inland sea located in the western part of Japan's southern island, Kyushu. The sea is bounded by the Uto Peninsula to the north, the Amakusa Islands to the west, and Nagashima Island to the south. On some maps it is also called the Yatsushiro Sea.

Minamata Bay is located on the eastern shore of the Shiranui Sea. It is bounded on the northwest by the Myojin promontory, and on the southwest by Koiji Island and the Modo promontory. At its south end is Fukuro Bay ("pouch" bay, so called for its shape). Leading into the northeast depth of Minamata Bay is the drainage channel of the Chisso Corporation's Minamata factory. (See map on page 179.)

Unusual changes were detected in these waters as long ago as 1950. Fish floated on the surface of the sea, shellfish frequently perished, and some of the seaweed died. In 1952 some birds such as the crow and the *amedori*—a type of sea bird— began to drop into the sea while flying. The area of the sea where dead fish could be seen floating spread throughout the bay and out into the Shiranui Sea. Sometimes octopus and cuttlefish floated so weakened that children could catch them with their bare hands.

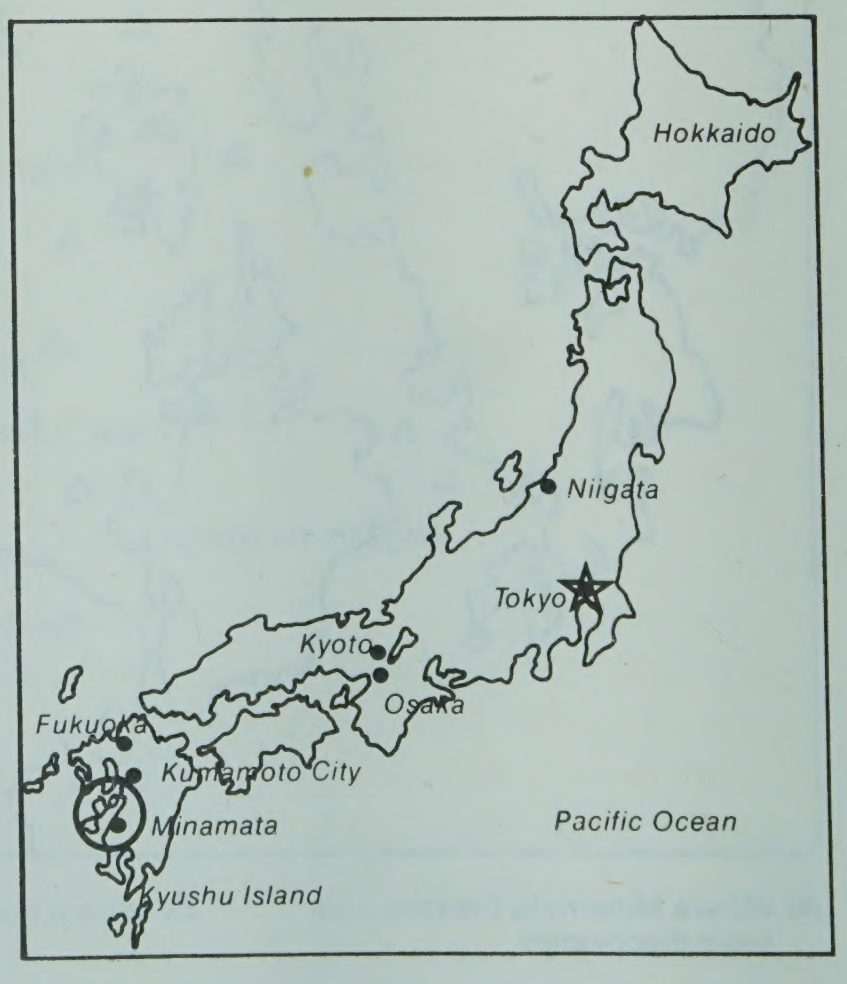
By 1953 not only cats but even some pigs and dogs went mad and died. The cats' "dancing disease"—called so by the local inhabitants—was particularly striking. Cats would stagger about as though drunk, salivating; convulsions would suddenly strike them or they would impulsively whirl in violent circles, often veering off without direction, often collapsing. So many cats died in this way that by 1957-58 there were virtually no cats to be found in the Minamata areas of Tsukinoura, Detsuki, Yudo and Modo!

Nevertheless, fish continued to live in Minamata Bay, fishermen continued to go out to catch them, and the people continued to eat them.

In April of 1956 a five-year, eleven-month-old girl entered the pediatrics department of the Chisso Corporation's Minamata factory hospital with brain-damage symptoms such as disturbance of gait, disturbance of speech and delirium. Within five weeks, her younger sister and four members of a neighbor family were found to be suffering from the same symptoms.

On May 1, 1956, Dr. Hajimé Hosokawa, the head of the Chisso factory hospital, reported to the Minamata Public Health Department: "An unclarified disease of the central nervous system has broken out." This is the official "discovery" date of what is now called Minamata Disease.

FIGURE 2 MAP OF JAPAN



Since the symptoms of those humans taken ill were similar to the symptoms of the cats, and since their cause was unknown, the local people immediately labeled the outbreak the "cats' dancing disease" or the "strange disease."

An immediate investigation by the Chisso factory hospital, the Public Health Department, the Minamata City Hospital, and the local medical association revealed that both children and adults were affected. This investigation quickly uncovered 30 cases. The investigators found that many of these people had been ill since about 1953, and that most lived in the fishing villages of Minamata. They had been diagnosed variously as having encephalitis Japonica (an inflammation of the brain caused by a virus), alcoholism, syphilis, hereditary ataxia, and a number of other suspected diseases. Because the outbreak was endemic, it was immediately linked to an infectious disease and treated as such. For physicians not familiar with methyl-mercury poisoning, these erroneous diagnoses were unavoidable.

In August, 1956, the Minamata Disease Research Group of the Kumamoto University Medical School was created to investigate the cause of the outbreak. This group made public its interim report on October 4, 1956. It had discovered that the "disease" was not infectious, and that it was a type of heavy-metal poisoning caused by eating the fish and shellfish of Minamata Bay.

At this point countermeasures should have been taken, since the causal *mechanism*—the fish and shellfish of Minamata Bay—was made clear. The government should have officially banned fishing and Chisso—the only possible source of such a large quantity of poison—should have temporarily stopped its production until the cause was found. Neither measure was taken.

The number of patients continued to increase rapidly. By late 1956 there were 52 known victims.

At the time, the Chisso waste water included various poisons, among them manganese, thalium, arsenic, mercury, selenium, copper and lead. The Kumamoto University Research Group found it necessary to conduct clinical, pathological, and experimental research on each poison.[2]

At first manganese was suspected. Then selenium. Then thalium.[3] Although large amounts of these poisons were detected in the environment and in autopsied patients, experiments with cats showed that none of these substances produced the same symptoms as the "strange disease." The manganese theory was maintained for some time by part of the group, but was finally rejected along with the others. Experiments were begun on the possibility that the causal element was a combination of several poisons. Results, however, were negative.

Even though the research group had not found the causal element, their experiments in 1957 began to prove the severity of contamination. Fish brought from outside the area rapidly accumulated poisons when nurtured in Minamata Bay, and when fed to cats, produced Minamata Disease symptoms in them. In one experiment, a group of cats was fed three times a day, and each meal of each cat was supplemented by about 40 tiny fish caught in Minamata Bay, weighing a total of 10 grams per meal. Within an average of 51 days, all the cats showed the symptoms. Other groups of cats brought in from other areas fell ill within a span of 32 to 65 days when fed fish and shellfish from Minamata Bay.[4]

As a result of detailed clinical examinations of patients, characteristic symptoms were found to be as follows: There were no prodromal (warning) symptoms, or fever. Symptoms began with a numbness of the extremities, difficulty in hand movements and in grasping things—such as buttoning buttons, holding chopsticks, writing—also lack of coordination, sensory disturbance, weakness and tremor, dysarthria (a speech disturbance due to damage of the cerebellum), ataxic gait, then disturbances of sight and impaired hearing. These symptoms gradually increased and finally caused general paraly-

TABLE 1 CLINICAL SYMPTOMS IN 34 CASES OF ACUTE AND SUB-ACUTE MINAMATA DISEASE
(H. TOKUOMI, 1959)

SYMPTOMS	%
Disturbance of sensation — superficial	100
Disturbance of sensation — deep	100
Constriction of the visual field	100
Dysarthria	88.2
Disturbances of coordination — adiadochokinesis	93.5
Disturbances of coordination — finger to finger and finger to nose (dysmetria)	80.6
Disturbances of coordination — ataxic gait	82.4
Romberg's sign	42.9
Impairment of hearing	85.3
Tremor	75.8
Tendon reflex — exaggerated	38.2
Tendon reflex — weak	8.8
Pathological reflexes	11.8
Salivation	23.5
Mental disturbances	70.6

sis, deformity, difficulty in swallowing, convulsions and even death. Of the first 52 patients discovered, 21 died within one year of the onset of the disease. Among them 16 died within three months and four died within six months[5] (see table 1)

Pathological findings were as follows:

Lesions in the cerebral cortex: Neurons of the cerebral cortex were generally damaged. The calcarine regions of the occipital lobe, the precentral cortex of the frontal lobe and the postcentral cortex of the parietal lobe were especially severely damaged. In acute cases, the cerebral cortex becomes spongy.

Cortical damage of the cerebellum: Granular cell-type atrophy in the depth of the cortical sulci was observed. While the Purkinje cells were more resistant to the intoxicant, they commonly disintegrated if heavily affected.

Damage of the peripheral nerves: The peripheral nerve fibers of the extremities, posterior root, and the column were selectively affected. Peripheral nerve fibers were the most severely affected.

The cerebral nuclei, brain stem and spinal cord revealed no remarkable lesions except for demyelination and gliosis of the pyramidal tracts[6]

Then in September of 1958 Professor T. Takeuchi of Kumamoto University found that clinical and pathological findings in cases of Minamata Disease coincided with certain cases of methyl-mercury poisoning reported in England in 1940 by D. Hunter and D.S. Russell[7] The English cases involved the poisoning of workers in a factory producing methyl mercury[8]

The Kumamoto University researchers began experiments with methyl mercury. Cats who were fed methyl mercury directly showed the same symptoms as those cats affected with Minamata Disease after eating the fish and shellfish of Minamata Bay.

The university researchers also conducted an environmental survey of mer-

cury for the first time. Findings showed in 1959 that there was an extraordinarily high level of mercury contamination in Minamata Bay: 2,010 parts per million (ppm) in the mud near the drainage channels of Chisso, the content gradually declining with the distance from the channel.[9]

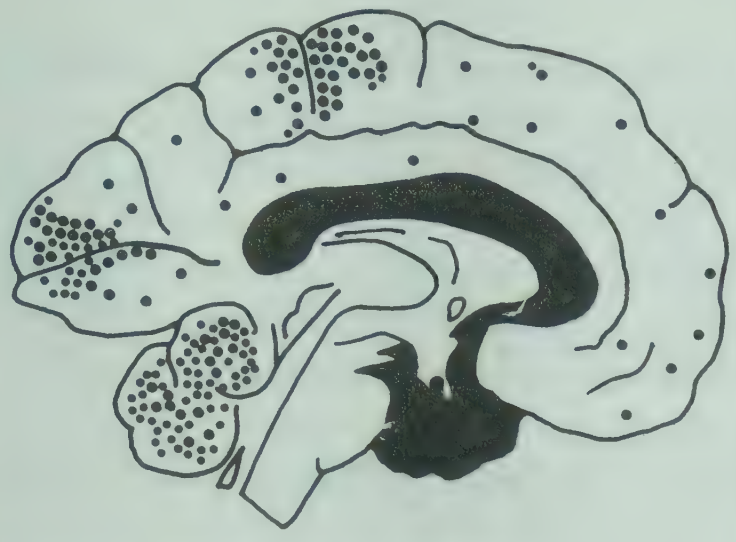
Fish and shellfish collected in Minamata Bay showed high mercury contents. 11.4-39.0 ppm[10] in Hormomya mutabilis, 5.61 ppm in an oyster, 35.7 ppm in a crab, 14.9 ppm in a Scioena schlegelii. Near the estuary of the Minamata River where the waste water was diverted in the fall of 1958 mercury levels were found to be 20.0 ppm in a short-necked clam (Venus japonica), 24.1 ppm in a fish called a Chinu, 10.6 ppm in a gray mullet (Mugil japonicus), etc.[11]

The cats in the area spontaneously affected by Minamata Disease and those cats experimentally affected by feeding fish and shellfish from Minamata Bay showed the following mercury levels: 37.0-145.5 ppm in the liver as compared with 0.9-3.66 ppm in the cats in a control group, 12.2-36.1 ppm (controls: 0.09-0.82) in the kidneys, 8.05-18.6 ppm (controls: 0.05-0.13) in the brain, and 21.5-70.0 ppm (controls: 0.51-2.12 ppm) in the hair.[12]

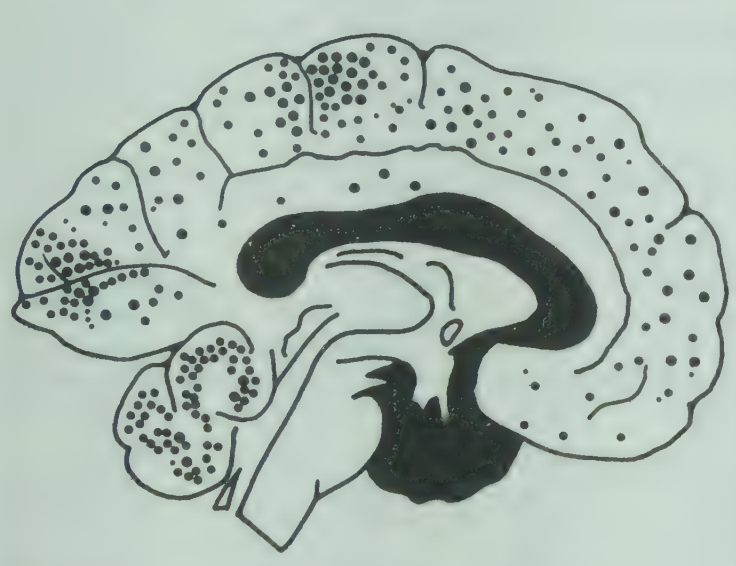
A high concentration of mercury was found in the internal organs of 23 persons who died of Minamata Disease (see table

FIGURE 3 PATHOLOGY OF MINAMATA DISEASE (T. TAKEUCHI, 1960)

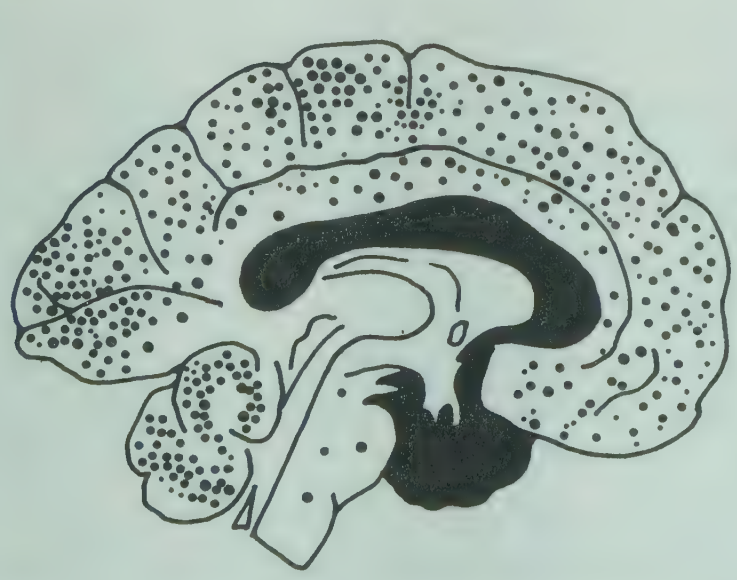
Comparison of the distribution of lesions among the adult, infant, and congenital infant victims of Minamata Disease.



Adult Minamata Disease

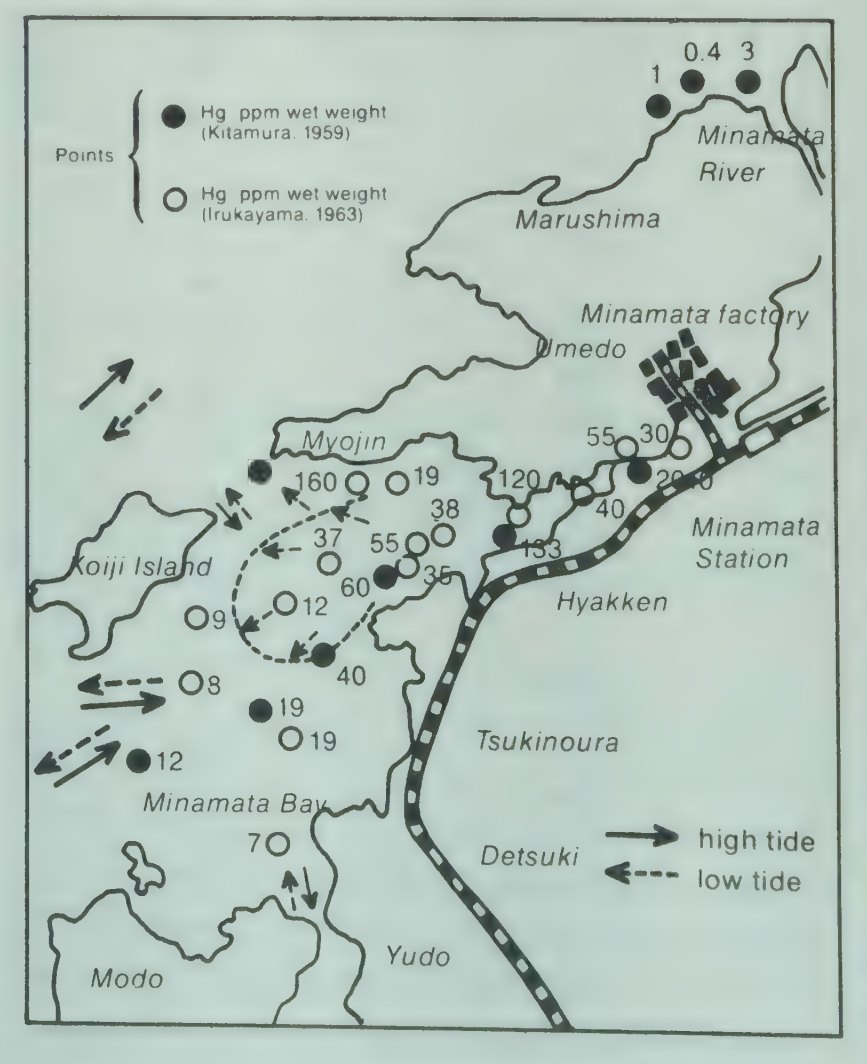


Non-congenital infantile Minamata Disease



Congenital Minamata Disease

FIGURE 4 MERCURY CONTENTS IN THE MUD OF MINAMATA BAY



2). The greatest amount was detected in the liver and kidney. Although the amount in the brain was less than in the liver and kidney, deposits were sufficient to cause severe brain damage; a characteristic of methyl-mercury intoxication is that the organic methyl mercury passes the blood-brain barrier more easily than does inorganic mercury, so the amount of deposit in the brain is larger than it would be in a case of inorganic mercury intoxication.[13]

A 1960 survey found a high mercury content in patients' hair, especially within one year after the onset of the disease: 96.8-705 ppm.[14] When fish was no longer consumed, levels gradually decreased with time. It is notable, however, that 100-191 ppm of mercury was detected in persons who were thought to be healthy.[15] The mercury content in the hair was equally high in the affected as well as some unaffected people at that particular time. This fact shows that the inhabitants in this area, even those in whom no symptoms had yet appeared, were all exposed to heavy mercury contamination (see table 3).

Later, in September of 1960, Professor M. Uchida of Kumamoto University extracted a methyl-mercury compound (CH_3HgSCH) in crystalline form from shellfish, Hormomya mutabilis, which had caused Minamata Disease.[16]

The causal element, methyl mercury, was now clear.

Now, however, Chisso counterargued that they used only inorganic mercury and not organic (methyl) mercury in their production process, and therefore they could not be the source of the contamination. In spite of Chisso's non-cooperation, the Research Group managed to find out at what point and in what way the inorganic mercury changed into organic mercury, followed the food chain to enter the fish, and then entered the human being.

Chisso at that time was using a large amount of inorganic mercury in their acetaldehyde and vinyl chloride manu-

TABLE 2 MERCURY CONTENT IN ORGANS OF HUMAN AUTOPSY CASES OF MINAMATA DISEASE (T. TAKEUCHI)

Number of Autopsy		Sex	Age	Clinical course (days)	Liver (ppm)	Kidney (ppm)	Brain (ppm)	$\frac{\text{Brain}}{\text{Liver}} \times 100$ (%)	$\frac{\text{Brain}}{\text{Kidney}} \times 100$ (%)
1	3159	♂	35	19	70.5	144.0	9.6	13.6	6.7
2	2774	♀	5	26	38.2	47.5	15.4	40.3	32.4
3	3350	♂	48	45	38.8	68.2	24.8	63.9	36.7
4	2791	♂	56	48	34.6	99.0	7.8	22.5	7.9
5	2776	♀	29	53	39.5	40.5	9.0	22.7	22.1
6	3201	♀	58	60	42.1	106.0	21.3	50.6	20.1
7	3349	♂	62	70	34.7	64.2	7.8	22.5	12.1
8	2775	♂	49	86	/	/	9.5	/	/
9	3209	♀	50	90	36.2	21.2	4.9	13.4	22.9
10	3388	♂	59	90	32.6	49.8	6.4	19.5	12.8
11	3355	♂	34	96	30.0	22.6	4.6	15.3	20.4
12	3290	♂	52	100	22.0	42.0	2.6	11.8	6.2
13	3497	♂	57	480	21.3	36.5	2.8	20.2	14.0
14	3018	♀	4.5	553	26.0	37.4	5.3		
15	3216	♀	8	993	6.4	12.8	1.3		
16	3139	♀	28	1000	2.1	3.1	0.1		
17	3298	♂	7	1467	5.4	5.9	2.2		
18	3567	♀	2.6	*	0.3	9.4	0.4		
19	3764	♀	6.4	*(years)	5.7	11.3	0.7		
20	3732	♂	60	2.0	8.3	19.6	1.0		
21	4292	♂	79	4.3	2.0	17.6	2.0		
22	4473	♂	78	9.9	35.0	12.6	3.0		
23	4312	♂	66	10.2	2.3	21.6	0		
Control (15 cases)					0–2	0–3	0–0.5		

TABLE 3 MERCURY CONTENT IN HUMAN HAIRS, 1959-60 (S. KITAMURA)

Patients of Minamata Disease				Healthy subjects in Minamata district	
Age, sex	Onset of disease	Date of hospitalization	Content in ppm	Age, sex	Content in ppm
61, male	Oct., 1959	Nov., 1959	436		12.7
46, male	Oct., 1959	Nov., 1959	705		0.0
56, male	July, 1959	Dec., 1959	350		1.82
44, male	Sept., 1959	—	411		31.0 (11.9)
33, male	Sept., 1959	Sept., 1959	281		191.0
61, male	Nov., 1959	Jan., 1960	431	Adult female	4.46
38, female	Aug., 1959	Sept., 1959	165		6.56
63, male	July, 1959	July, 1959	170		72.9
49, male	Mar., 1959	Mar., 1959	96.8		65.4
43, male	Oct., 1956	Oct., 1959	21.6		101.0 (60.0)
50, male	Sept., 1956	Sept., 1956	13.2		39.1
35, female	Sept., 1956	May, 1957	3.60		16.0
18, male	July, 1956	—	39.2		17.1
29, male	July, 1956	Aug., 1956	15.8		24.3
17, female	June, 1956	July, 1956	29.4	Boy	61.0
9, female	June, 1956	—	2.46		48.4
49, female	May, 1956	—	30.0		13.0
20, female	May, 1956	July, 1956	18.0	Girl	11.5
45, female	May, 1956	Aug., 1956	3.01		4.16
22, female	Apr., 1956	—	16.4		
6, female	Apr., 1956	—	18.0		
10, female	Apr., 1956	—	165		
56, male	Apr., 1956	July, 1956	16.1		
18, female	Aug., 1954	—	4.25		
23, male	Aug., 1954	—	12.7		

Healthy subjects outside of Minamata district	
Age, sex	Content in ppm
Adult male	3.48
	0.75
	4.42
	1.39
Adult female	1.61
	1.25
	2.07
	0.14
	1.63
	2.13
	2.86
	2.15
Girl	7.49
	0.64
	2.30
	2.31

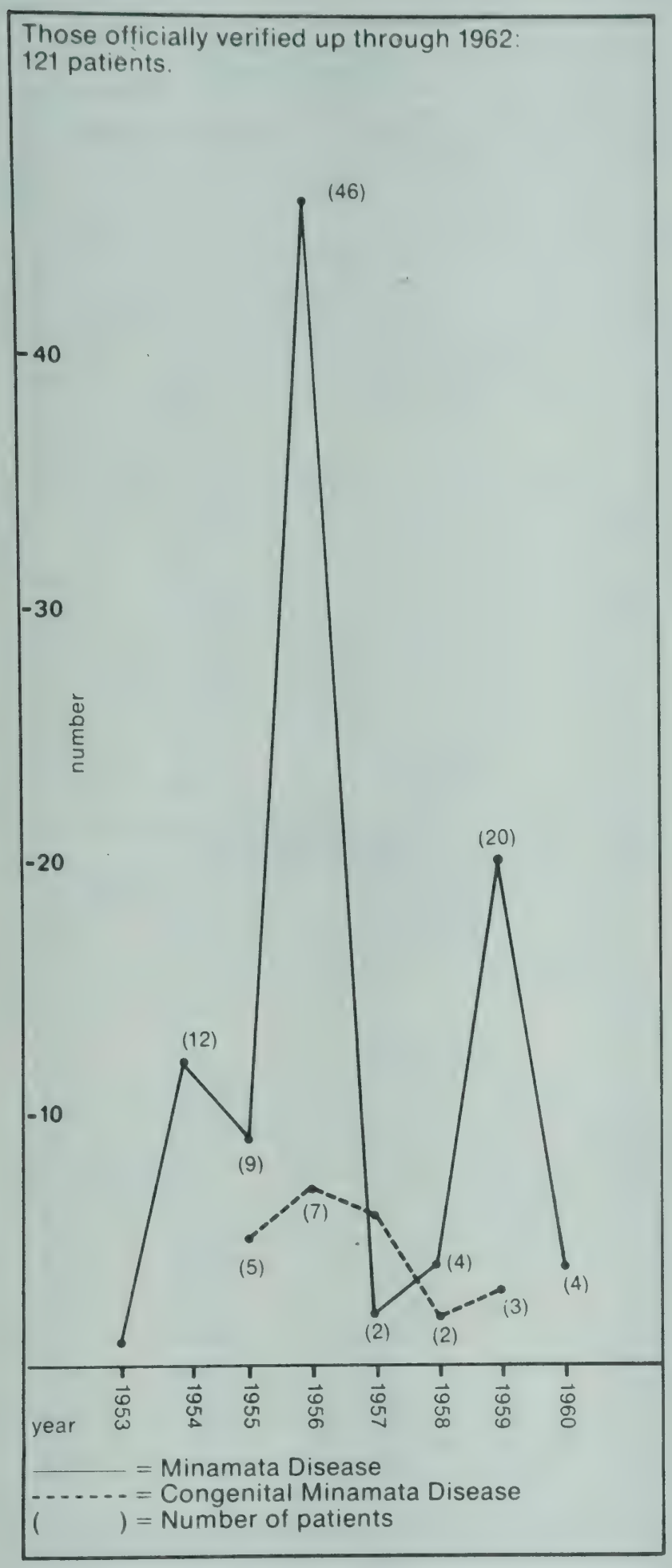
Note: Number in parenthesis denotes the content in nails.

facturing process. (According to one estimate made later, the total mercury dumped by Chisso could be 200 to 600 tons.) However, after the presentation of the mercury theory, Chisso became obstinate, and factory waste water became impossible to obtain for experimental purposes.

Finally in the fall of 1962, Dr. K. Irukayama of Kumamoto University found in a laboratory, left over from the time when Chisso had been more cooperative, a bottle of sludge from the acetaldehyde process.[17] In their sludge he detected methyl-mercury chloride (CH_3HgCl), therefore proving that the factory process itself had methylated the inorganic mercury.

These findings proved beyond a doubt that the inorganic mercury used as catalyst in the acetaldehyde process had methylated inside the factory and had entered Minamata Bay. The waste of the acetaldehyde process continued to pour into the bay until 1968.[18] It was later learned that by the end of 1959 Dr. H.

FIGURE 5 ANNUAL ONSET OF MINAMATA DISEASE



Hosokawa of Chisso's factory hospital had proven that the acetaldehyde sludge itself fed directly to cats caused the same symptoms as Minamata Disease. This fact was never made public by Chisso.

The number of patients continued to increase.

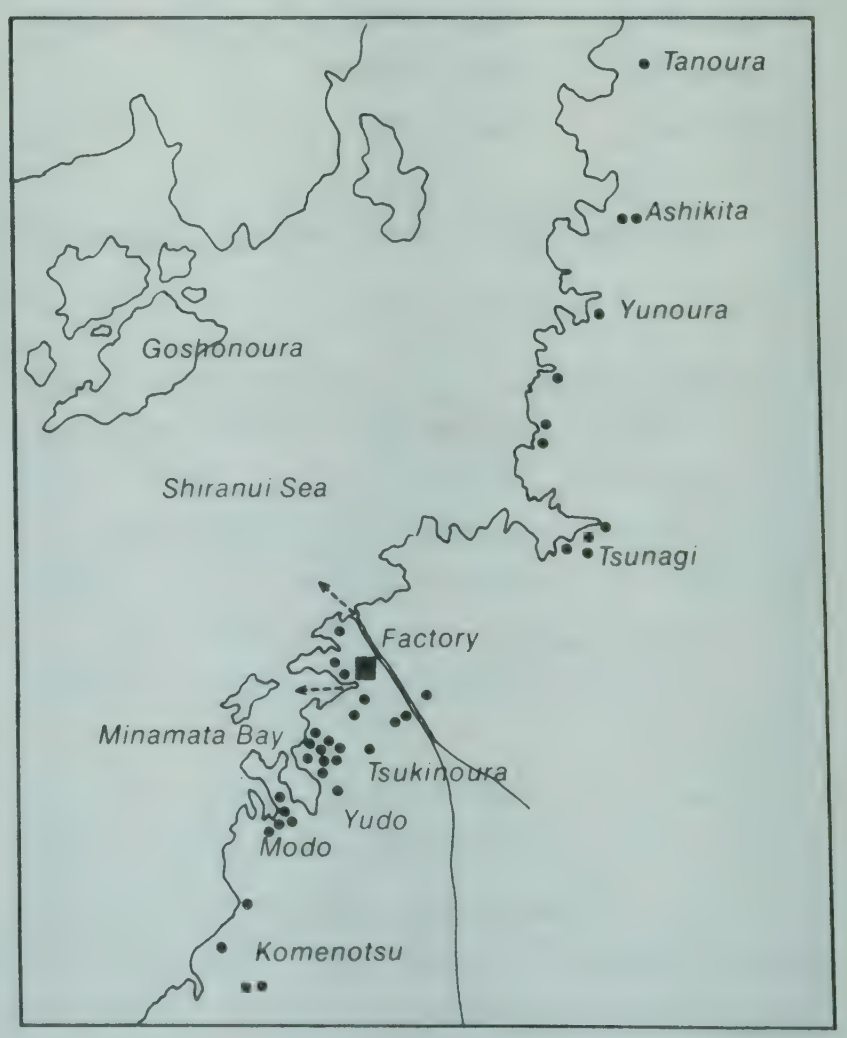
At this point—the end of 1962—there were 121 officially verified Minamata Disease patients, of whom 46 had died.

Congenital Minamata Disease

A major question still remained unanswered by the researchers. Many cases of congenital idiocy accompanied by various neurological symptoms had broken out on the coast of Minamata during the same period as the outbreak of Minamata Disease. From the beginning it was suspected that these children might be cases of Minamata Disease.[19] Since none of them had eaten the fish and shellfish of Minamata Bay these children affected from birth were generally diagnosed as having cerebral palsy. In none of these cases, however, could there be found abnormal factors during the mother's pregnancy, at delivery, or in the postnatal period that might have caused cerebral palsy; the one common and notable factor was that the mothers of these children had all eaten a great deal of the fish and shellfish of Minamata Bay during their pregnancy.

The clinical characteristics of these children consisted of serious mental retardation, primitive reflexes such as oral reflex and grasping reflex, cerebellar symptoms of asynergy such as disturbance of coordination, ataxia, adiadochokinesis, dysmetria, intention tremor,

FIGURE 6 DISTRIBUTION OF CONGENITAL MINAMATA DISEASE, 1974 (M. HARADA)



dysarthria, nystagmus. They also manifested disturbance of growth, akinesia, hypokinesia, hyperkinesia (chorea, athetosis, etc.), salivation, character disorder (unfriendly, indifferent, shy, nervous and restless, excited and obstinate), psychomotor seizure, loss of consciousness, myoclonic jerk, grand mal epilepsy, and also deformity of limbs, strabismus, and pathological reflex[20]

The clinical picture of these patients was similar to certain symptoms in cases of exogenous idiocy, serious feeble-minded physically handicapped infants, and cerebral palsy. But when a comparison was made between the symptoms of the Minamata cases with those having similar diseases in other parts of Japan, the Minamata cases stood out as unique. It was found that in instances of exogenous idiocy caused by other factors, cerebellar symptoms and strabismus were rarely observed but pathological reflex (pyramidal signs) was remarkable. In general among cerebral palsy patients, as compared to these Minamata patients, intelligence disturbance was slight, cerebellal symptoms were rarely observed, but hyperkinesia (particularly chorea and athetosis) was remarkable.

Of the 220 births between 1955 and 1958 in the Tsukinoura, Detsuki, Yudo and Modo districts (the Minamata areas most affected by Minamata Disease), 13 such cases were found by 1962—a rate of 5.9%. This is much higher than the 0.2-0.3% rate of cerebral palsy cases in other areas of Japan.

A check was made on their families. In 1962, 64% of these children had some member of their family who had typical acute Minamata Disease. All the mothers of these patients were thought to be healthy at the time. However, when carefully observed certain neurological symptoms were present in 73% of the mothers: for example, ataxia, adiadochokinesis, nystagmus, dysarthria, sensory disturbance. Ten years later, these symptoms were observed to have increased.

The mercury content in the hair of these children who were born between 1955 and 1958 was still high in 1961. For example, one child's hair registered 100 ppm. The mercury content in the hair of the mothers who had given birth to

TABLE 4 COMPARISON OF CLINICAL SYMPTOMS AND SIGNS IN CONGENITAL MINAMATA DISEASE, EXOGENOUS IDIOCY, AND INFANTILE CEREBRAL PALSY, 1962 (M. HARADA)

	No. of Cases	Congenital Minamata Disease (%)	Exogenous idiocy (%)	Infantile cerebral palsy (%)
Intelligence disturbance	17	100	100	25
Primitive reflex	17	100	61	31
Cerebellar abnormalities	17	100	33	18
Extrapyramidal abnormalities such as chorea, athetosis	16	94	72	100
Hypersalivation	16	94	32	68
Paroxysmal disorders	14	82	66	0
Strabismus	13	76	11	37
Pyramidal abnormalities (spastic paralysis)	12	71	100	43
Asymmetry of symptoms and signs	0	0	72	18
Causative factor present	0	0	50	62

Causative factors in the cases of exogenous idiocy and infantile cerebral palsy: abnormal pregnancy, fever, trauma, etc.

these children was also as high as 191.0 ppm and 172.9 ppm in some cases?[21] The preserved umbilical cords of these children had higher methyl mercury contents than those of other children?[22]

Then in 1961 and 1962 two of these children died. The autopsies gave significant findings. Typical pathological findings found in methyl-mercury poisoning cases (such as granular cellular atrophy in the cerebellum) were observed. Also microcephalia, general hypoplasia of the medullary substance (subcortex), hypoplasia of the corpus callosum and hypoplasia of the pyramidal tract were found, thereby showing that damage occurred in the early fetal stages?[23]

The clinical, epidemiological, and pathological findings indicated that methyl mercury had passed through the placenta from the mother to the fetus, thereby causing methyl-mercury poisoning. This was diagnosed as congenital (fetal) Minamata Disease in 1962. At present (1974), 40 such congenital cases have been found.

Furthermore, autoradiographical experiments on pregnant animals and histological study of their embryos later showed that methyl mercury passed through the placenta and caused damage to the central nervous system in the embryos?[24]

The methyl-mercury content in the milk of mothers who have been contaminated by methyl mercury has been proven to be high?[25] Since the ingestion of milk containing methyl mercury causes poisoning,[26] it cannot be denied that congenital cases may also have been affected by their mothers' milk after birth.

Treatment

Cells of the central nervous system that have once been damaged do not recover.

During the initial acute stage of the disease, various medicines (BAL, D-Penicillamine, EDTA-Ca and Alpha-Mercaptopropionyl glycine) were used to excrete the mercury from the body.

Later, vitamin B-complex in large dosages was used to activate the metabolism of the nerves that remained relatively undamaged.

The above methods of treatment showed only limited success. By the time of the occurrence of symptoms, much of the damage had already occurred.

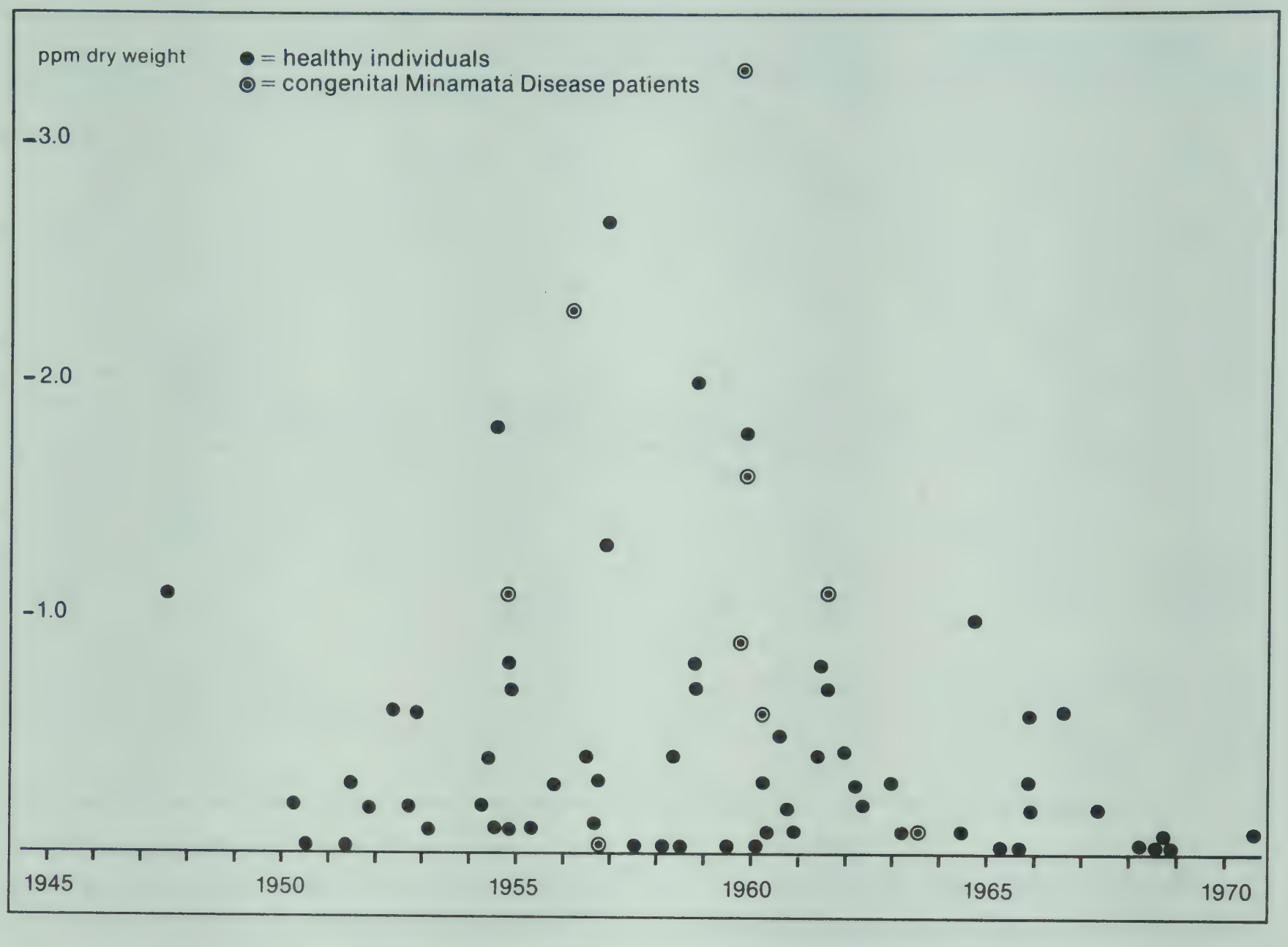
The forms of treatment in the chronic stage—the predominant stage at present—are rehabilitative, physical, and allopathic treatment. To be of any help at all, rehabilitative treatment must be done on a case-by-case basis. This form of treat-

TABLE 5 FREQUENCY OF SYMPTOMS IN CONGENITAL MINAMATA DISEASE CASES, 1971 (M. HARADA)

	Number of Cases	%
Intelligence disturbance	25	100
Dysarthria	24	96
Extrapyramidal hyperkinesia & hypokinesia	23	92
Cerebellar symptom	19	76
Deformation of limbs	21	84
Primitive reflex	18	72
Strabismus	18	72
Hypersalivation	18	72
Paroxysmal symptom	9	36
Pathological reflex	12	48
Inhibited bodily growth	17	68

Note: 3 cases out of 29 have died. 25 of the 29 cases were examined.

FIGURE 7 METHYL MERCURY FOUND IN UMBILICAL CORDS IN THE MINAMATA AREA



ment has had some good results on young and light cases, but is limited in its effectiveness. The younger the patient, the better the chances for improvement in symptoms of ataxia, dysarthria, and tremor. In the congenital cases (except for the most severe) there is some improvement of ataxia, primitive reflex and disturbance of intelligence. Physical treatment involves massage, hot spring baths, acupuncture and moxibustion, all with limited success; effectiveness is often temporary and varies significantly among individuals.[27] When hypertension, dysfunction of the liver and kidneys and other symptoms exist, treatment of these symptoms is obviously necessary.

The complaints of the patients vary, and are numerous. Therefore allopathic treatment is also very important. Their complaints are as follows: numbness (of feet, hands and around the mouth), a kind of tingling numbness, a smarting, languidity, heaviness, dullness, pain (of head, shoulders, hands, feet, the small of the back), heaviness of the head, especially the back part, a blurry dimness of the eyes, difficulty in seeing surroundings (due to vision constriction), difficulty in hearing, ringing in the ears, difficulty in tasting, difficulty in smelling, easily stumbling, falling, difficulty in putting slippers on, the fingers not moving well, easily dropping things, difficulty in buttoning one's clothes, words becoming entangled and knotted, difficulty in mouthing words, lack of strength, cramps, muscle twitch, tremor, sleeplessness, tiring easily, not wanting to do anything, forgetfulness, lack of ability to concentrate, swooning, fainting.

Even though many are able to move about and do some work, the patients experience a great deal of handicap in their daily lives.

Since the methods of treatment are very limited, and there is no way of healing the symptoms, there is need for psychological support as well as rehabilitative, physical and allopathic treatment.

TABLE 6 MERCURY CONTENT IN HAIR OF HEALTHY FISHERMEN, 1960

ppm	~1	1~10	10~50	50~100	100~150	150~200	200~300	300~	Total
Minamata	7	31	100	49	11	1			199
Tsunagi		12	61	23	4	2			102
Yunoura			14	9	1				24
Ashikita		1	19	19	1				40
Tanoura		6	15	11					33
Ryugataké	2	22	57	5		1			87
Goshonoura	6	53	334	75	11	1		2(357, 920)	482

ppm	~20	20~50	50~100	100~200	200~300	300	Total
Komenotsu	185	117	105	37	5	1 (624)	445
Akuné	26	4	1	3		1 (338)	33
Takaono	2	3	5				10
Higashi Town	18	32	23	2 (142)			75
Kumamoto City (control)	4 18	9	0	0	0	0	31

Note: ( ) = ppm

Chronic cases of Minamata Disease

The main typical symptoms of Minamata Disease found originally are still present in 1974 in high degree among very many patients, indicating that these main symptoms are difficult to improve. However, there are differences among individuals. When each symptom is examined closely, improvement can be seen in some individuals, and worsening in others. This also varies, however, from symptom to symptom.

Generally among adults there has been improvement in ataxia, dysarthria, tremor and hyper-salivation, and a worsening in pyramidal symptoms, muscular atrophy, and mental disturbance.

Generally among infantile and congenital cases, there has been improvement or even a disappearance of ataxia, hypersalivation, primitive reflex and paroxysmal symptoms, but mental disturbance remains and becomes predominant.

Therefore, with the passing of years, there is a tendency of these formerly typical cases to become incomplete or atypical cases of Minamata Disease[28]

In the chronic cases of Minamata Disease that have recently been discovered, the basic symptoms are vision constriction and sensory disturbance, but dysarthria and ataxia are relatively slight or nonexistent. Pyramidal symptoms and muscular atrophy and mental disturbance, however, are predominant?[29]

These facts coincide with the recent pathological findings of chronic cases conducted by Dr. T. Takeuchi: Brain damage is more diffused throughout the entire organ than it was in earlier patients. Brain damage and nerve cell atrophy, as well as degeneration of the pyramidal tract of the spinal cord, have also been found?[30]

Awakening to the "Non-Conclusion" of Minamata Disease

During the years 1962 to 1970 it was generally believed that Minamata Disease had been "concluded." It was believed that the number of patients was 121, that they had fallen ill between the years 1953-1960, and that the outbreak had occurred in the 50-kilometer area north and south along the coast of Minamata?[31]

Chisso continued, however, to emit

TABLE 7 NEUROLOGICAL SYMPTOMS OBSERVED AMONG FAMILY MEMBERS OF OFFICIALLY VERIFIED PATIENTS, 1971 (M. HARADA)

	Family members	Mothers of congenital Minamata Disease patients
Sensory disturbance (Total)	115 (79%)	21 (100%)
extremities	109 (75%)	21 (100%)
perioral	44 (30%)	4 (19%)
Incoordination (Total)	94 (65%)	16 (76%)
Ataxic gait	47 (32%)	10 (48%)
Finger-Nose test	69 (48%)	11 (52%)
Adiadochokinesia	90 (62%)	16 (76%)
Romberg's sign	20 (14%)	6 (29%)
Dysarthria	65 (45%)	9 (43%)
Constriction of the visual field	53 (37%)	10 (48%)
Auditory disturbance	80 (55%)	16 (76%)
Tremor	51 (35%)	6 (29%)
Chorea and athetosis	2 (1%)	0
Muscular weakness	37 (26%)	7 (33%)
Muscular rigidity or spasticity	43 (30%)	7 (33%)
Hyperreflexia	42 (30%)	7 (33%)
Pathologic reflexes	11 (8%)	2 (10%)
Muscular atrophy	16 (11%)	0
Hypersalivation	8 (6%)	0
Vegetative symptoms	43 (30%)	12 (57%)
Deformities of the extremities	27 (19%)	1 (5%)
Pain	52 (36%)	8 (38%)
Intelligence disturbance	67 (46%)	14 (67%)
Total examined	145 (100%)	21 (100%)

waste water containing mercury until May of 1968. Also, when Chisso had diverted its waste water to the Minamata River for a period in September of 1958, the mercury contamination had spread out to a part of the Shiranui Sea north of Minamata. According to data gathered from healthy fishermen in 1960, mercury contamination had spread to even Goshonoura and Shishi Island.[32] Cats had fallen ill with Minamata Disease, and the mercury content of the inhabitants' hair was high.

Moreover, it began to be believed that the installation of a Cyclator by Chisso in December of 1959 meant no more poison was entering the sea, although it was found out later that the system did not prove effective in taking out the mercury.

From around 1962, the inhabitants began to eat the fish again. Although it seems unbelievable, the government did nothing.

At present there are plans for dredging and for filling in part of the contaminated area. The sludge at the bottom of the bay still has a mercury content of 25-200 ppm. Also, some of the fish and shellfish of Minamata Bay still have mercury contents above the official safety level.

Therefore, it is not surprising that even after 1960 there were people whose symptoms worsened, and people in whom symptoms appeared for the first time—or that there was a widening of the area in which patients appeared.

The full extent of Minamata Disease had remained hidden between 1962 and

TABLE 8 FREQUENCY OF NEUROLOGICAL SYMPTOMS IN INHABITANTS OF MINAMATA, GOSHONOURA AND ARIAKÉ AREA, 1973 (SECOND MINAMATA DISEASE RESEARCH GROUP)

	Minamata (Tsukinoura, Yudo, Modo)	Goshonoura	Ariaké (control)
Sensory disturbance	260 (28.0)	132 (7.6)	94 (10.3)
Incoordination (Total)	228 (24.7)	193 (11.2)	122 (13.4)
Ataxic gait	84 (9.0)	50 (2.9)	20 (2.2)
Adiadochokinesia	171 (18.4)	101 (5.8)	50 (5.5)
Finger-nose test	106 (11.4)	28 (1.6)	11 (1.2)
Dysarthria	114 (12.2)	63 (3.6)	18 (1.9)
Auditory disturbance	272 (29.2)	156 (9.0)	135 (14.9)
Constriction of the visual field	127 (13.7)	47 (2.7)	9 (0.9)
Tremor	94 (10.1)	87 (5.0)	27 (2.9)
Pathologic reflexes	56 (6.0)	34 (1.9)	21 (2.3)
Hemiplegia	17 (1.8)	9 (0.5)	10 (1.1)
Pain (limbs)	128 (13.7)	92 (5.3)	74 (8.1)
Epileptic seizure	26 (2.8)	19 (1.1)	8 (0.8)
Muscular atrophy	55 (5.9)	13 (0.7)	7 (0.8)
Parkinsonismus	23 (2.5)	13 (0.7)	7 (0.8)
Deformities of limbs	81 (8.7)	104 (6.0)	73 (7.8)
Intelligence disturbance	211 (22.7)	178 (10.3)	98 (10.8)
Hypertension	218 (23.4)	237 (27.5)	180 (19.1)
Total	928 (100.0)	1723 (100.0)	904 (100.0)

Note: Minamata percentages exclude the 3.9% of patients already verified in the Tsukinoura, Yudo, and Modo areas of Minamata.

1971 for the following reasons:

Only the prefecturally appointed committee members of the Minamata Disease Verification Committee could officially diagnose patients as having Minamata Disease. The inhabitants, however, did not know how to apply for official verification.

The stigma which Minamata Disease carried was so great that no one wanted to be verified as a patient.

The fishermen, fearing that their fish might not sell, kept quiet.

Many, believing that Minamata Disease was a thing of the past, thought their illness was from other causes.

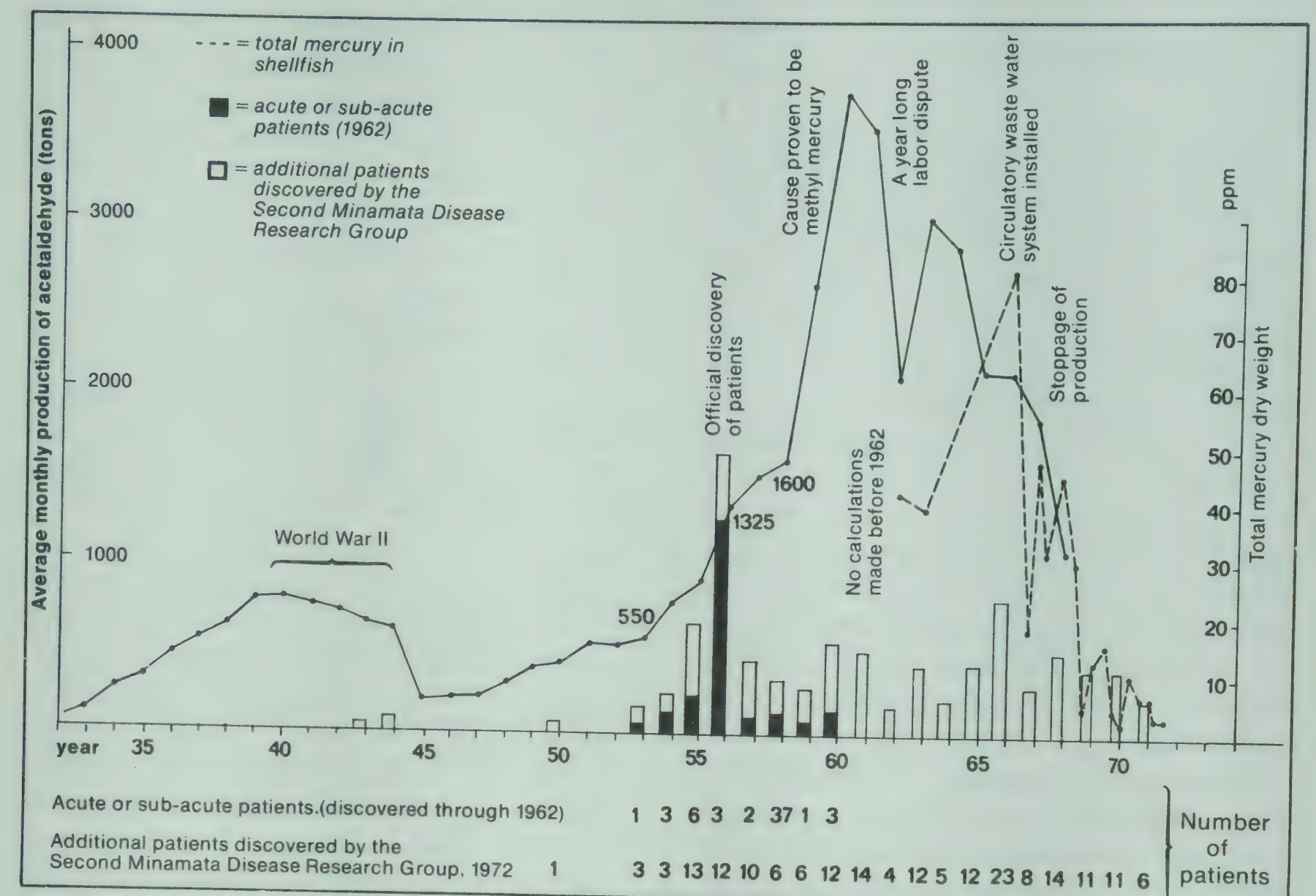
The government did not pursue any research whatever.

As a result, the fact of continued contamination did not come to the surface until 1971.

Medically, up to then, the only cases diagnosed as Minamata Disease were acute, severe cases and cases which showed the typical methyl-mercury symptoms reported by Hunter and Russell[33] Slight cases and those with incomplete sets of symptoms were excluded. Also, since it was believed that Minamata Disease was over, even those who slowly began to manifest the full set of symptoms of typical methyl-mercury poisoning after 1960—no matter how typical and severe their case—were not thought to be affected by Minamata Disease.

However, since "Minamata Disease" is really the methyl-mercury poisoning of the people of this whole area through environmental contamination, it should have been theorized that the typical chosen cases were probably only the tip of the iceberg, and that there could be still many undiscovered patients. In a case such as this, where the inhabitants of an entire area are subjected to methyl-mercury contamination, one cannot clarify the effect this contamination has had upon them by picking up only those who display a clear set of typical symptoms.

FIGURE 8 COMPARATIVE CHART OF ACETALDEHYDE PRODUCTION RATE, ONSET OF MINAMATA DISEASE, AND MERCURY CONTENT IN THE SHELLFISH OF MINAMATA BAY


Average monthly production of acetaldehyde (tons)
4000
3000
2000
1000
- - - = total mercury in shellfish
■ = acute or sub-acute patients (1962)
□ = additional patients discovered by the Second Minamata Disease Research Group
World War II
Official discovery of patients
Cause proven to be methyl mercury
A year long labor dispute
Circulatory waste water system installed
Stoppage of production
No calculations made before 1962
550
1325
1600
ppm
Total mercury dry weight
80
70
60
50
40
30
20
10
year 35 40 45 50 55 60 65 70
Acute or sub-acute patients.(discovered through 1962) 1 3 6 3 2 37 1 3
Additional patients discovered by the Second Minamata Disease Research Group, 1972 1 3 3 13 12 10 6 6 12 14 4 12 5 12 23 8 14 11 11 6
Number of patients

Note: These patients are those limited to the Tsukinoura, Detsuki and Yudo areas. Shellfish are Venus Japonica off Koiji Island (Fujiki)

In 1970, surveys were begun again by individual medical researchers.[34] As a result, it gradually became clear that the influence of methyl mercury on the population in general was much greater than was assumed before.

Since family members of the patients with typical Minamata Disease had been eating the same contaminated fish, they were examined first. It was found that 84% of these individuals had some symptom connected with Minamata Disease, and 55% had some neuropsychiatric disturbance in their daily life.[35]

It was also found that the mothers of the congenital patients all suffered symptoms, but that their symptoms were generally lighter than those of other family members.[36] Also, women who had had miscarriages and stillbirths were found to have relatively lighter symptoms than other members of their families; it was suggested that methyl mercury was discharged from their bodies through the placenta and into the fetus.

By March 1971, social awareness of the potentials of pollution had grown significantly, and the Second Minamata Disease Research Group was established at Kumamoto University by Kumamoto Prefecture.

Health surveys conducted by the Second Research Group in the most severely contaminated Minamata areas of Tsukinoura, Detsuki, and Yudo showed sensory disturbance among 28% of the inhabitants, disturbance of coordination among 24%, dysarthria in 12%, auditory disturbance in 29%, constriction of the visual field in 13%, tremor in 10%, and other neuropsychiatric symptoms as detailed in Table 8. These figures do not include the 37 cases already officially designated in this area.[37]

The above figures indicate that the neurological symptoms among the inhabitants of this area are clearly more common than they are in a control group from Ariaké, an area of Kyushu assumed not to be contaminated by methyl

mercury?[38]

Moreover, the survey showed that the appearance of symptoms was not limited to the 1953-1960 period as was thought before.

Since the rate of appearance of typical Minamata Disease neurological symptoms runs parallel to the rate of contamination—the greater the level of contamination in the area, the higher the frequency of symptoms—the survey concluded that the symptoms must stem from the effects of mercury. In addition, some neurological symptoms such as were seen at a high rate among those muscular atrophy, epileptic seizure and pain of the limbs, which were *not* previously attributed to Minamata Disease, surveyed in the Minamata area. These symptoms could be considered the chronic forms of methyl-mercury poisoning.

Even in the Goshonoura area, where no patients had been discovered until 1972, the effect of methyl-mercury contamination on humans was found. Since 1973, 12 Minamata Disease patients have been officially identified in this area.

Therefore, even in such limited surveys as have been described above, methyl-mercury contamination was found and cases of Minamata Disease—hidden up to then—were revealed.

There are approximately 100,000 inhabitants living on or near the shores of the Shiranui Sea. One can only speculate on how many have been affected by this mercury contamination.

By December 1974, there were 798 officially verified patients, of whom 107 had died. Some 2,800 more are applying for verification.

A Schematic View of Minamata Disease[39]

The effects of methyl mercury on the human body vary according to the degree of contamination.

When methyl mercury enters the body rapidly in large doses, death follows the appearance of acute brain-damage symptoms such as disturbance of consciousness, convulsion and paralysis. When methyl mercury intake is less, it causes reported by Hunter and Russell. When the dose is even less, symptoms appear light or atypical or incomplete, as in the chronic type of Minamata Disease. When intake is even less, symptoms may appear as a non-specific disease, for example hypertension or hepatitis. When even less, the symptoms may remain latent.

Previously it was thought that the effect of methyl mercury was predominantly upon the nervous system. This is definitely so. It has become evident, however, that the effect of methyl mercury on other human organs must be considered. For example, disturbance of liver function, diabetes, and hypertension are greater in the contaminated area than the control area. The survey results showed that among all the inhabitants surveyed in the Minamata area of Tsukinoura, Detsuki and Yudo, liver function tests such as urobilinogen registered positive among 6.5%, GOT among 20.7%, GPT among 17.6%. Hypertension (systolic pressure over 150) was found in 47% of those over 40?[40] Indeed, autopsies of acute or subacute cases have shown damage by methyl mercury to the liver, kidneys, pancreas and bone marrow?[41]

Since the neurological symptoms of Minamata Disease are so predominant, the focus had been on these symptoms; metabolic and functional examinations still remain insufficient.

In the schematic view of congenital Minamata Disease, if the mother's methyl mercury intake is so great that she falls acutely ill with Minamata Disease, she does not become pregnant. If the dosage is somewhat less, the woman becomes pregnant but the child is spontaneously aborted or is born dead. If the dosage is even less, a child with congenital Minamata Disease, accompanied by severe neurological symptoms, is born. Even in such cases, the mother's own symptoms may be relatively light. If the mother's mercury dosage is even less, there is a chance that the child—even with no remarkable neurological symptoms—may be mentally deficient. In such cases the mother may have almost no neurological symptoms. It would be difficult to differ-

FIGURE 9 1962: 121 OFFICIALLY VERIFIED PATIENTS

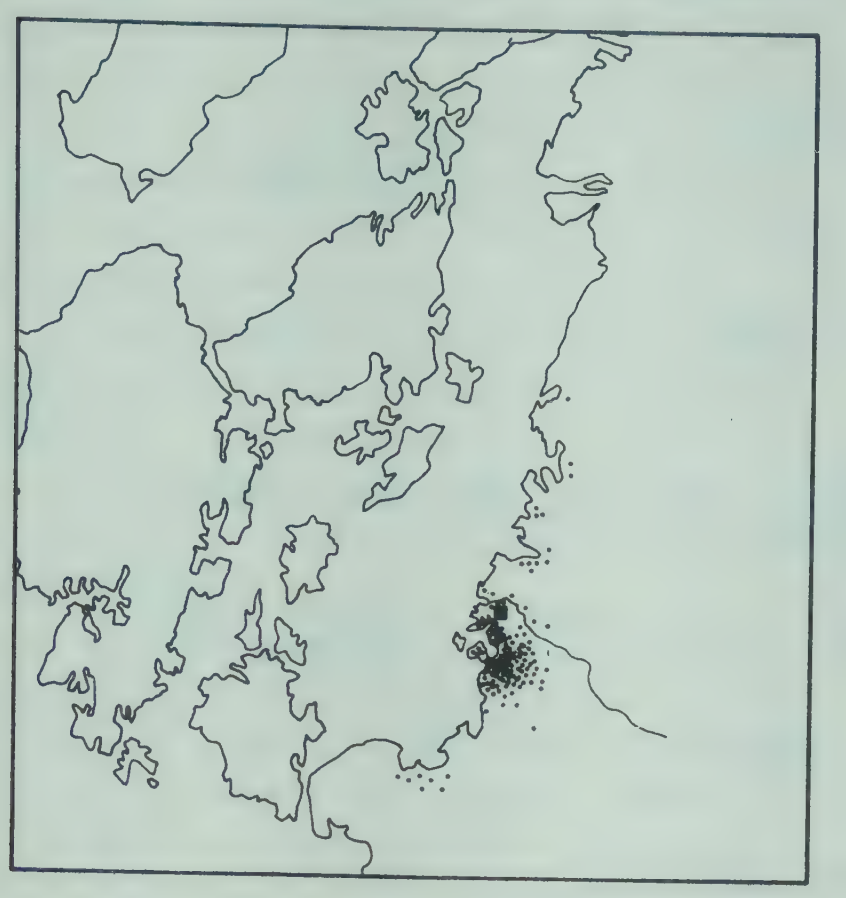
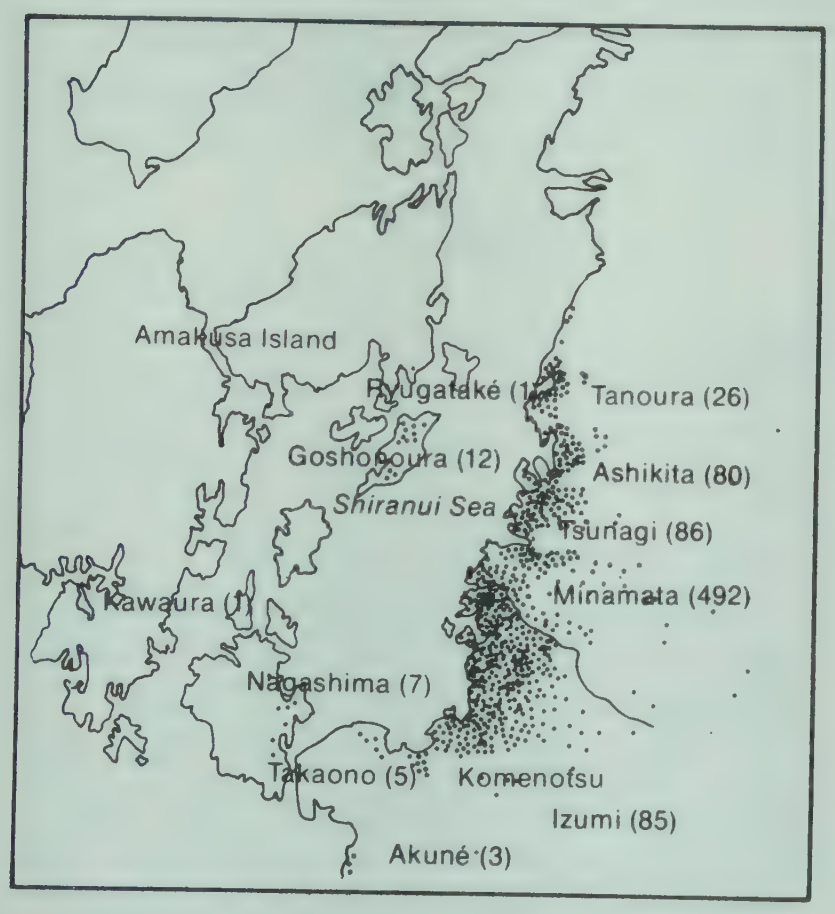


FIGURE 10 DECEMBER 1974: 798 OFFICIALLY VERIFIED PATIENTS



entiate the symptoms of these children from mental deficiency due to a different cause?[42]

As a matter of fact, in the most heavily contaminated Minamata area of Tsukinoura, Yudo and Modo, mental deficiency among children born between 1955-1959 was 29% (1962). This figure excludes the already recognized congenital cases. It is astonishingly higher than in the control area?[43]

Moreover, in 1970 an examination of junior high school students in this contaminated area was made, and 223 children born between April of 1955 and March of 1958 were examined. These children are attending regular public school classes and do not include the already recognized congenital cases. The following observations were made. Mental deficiency was found among 18%, sensory disturbance among 21%, clumsy speech among 12%, and clumsy movements among 9%. These examinations were conducted by qualified neuropsychiatrists directly examining the children. These rates are higher than in any other part of Japan examined.[44]

The schematic views of Minamata Disease and congenital Minamata Disease indicate that there are types and levels of methyl-mercury poisoning that are as yet undefinable, undetectable, or unknown in our present medical practice. In Minamata the levels of poisoning were so great that the heavier dosages of contamination could be readily detected. It is quite possible, however, that in other areas with lower levels of contamination, symptoms may go undetected as methyl-mercury poisoning. The world-wide implications of the possible effects of long-term, low-level poisoning become self-evident. We must examine the present concept of a "safe" level of methyl mercury consumption.

Safety Level

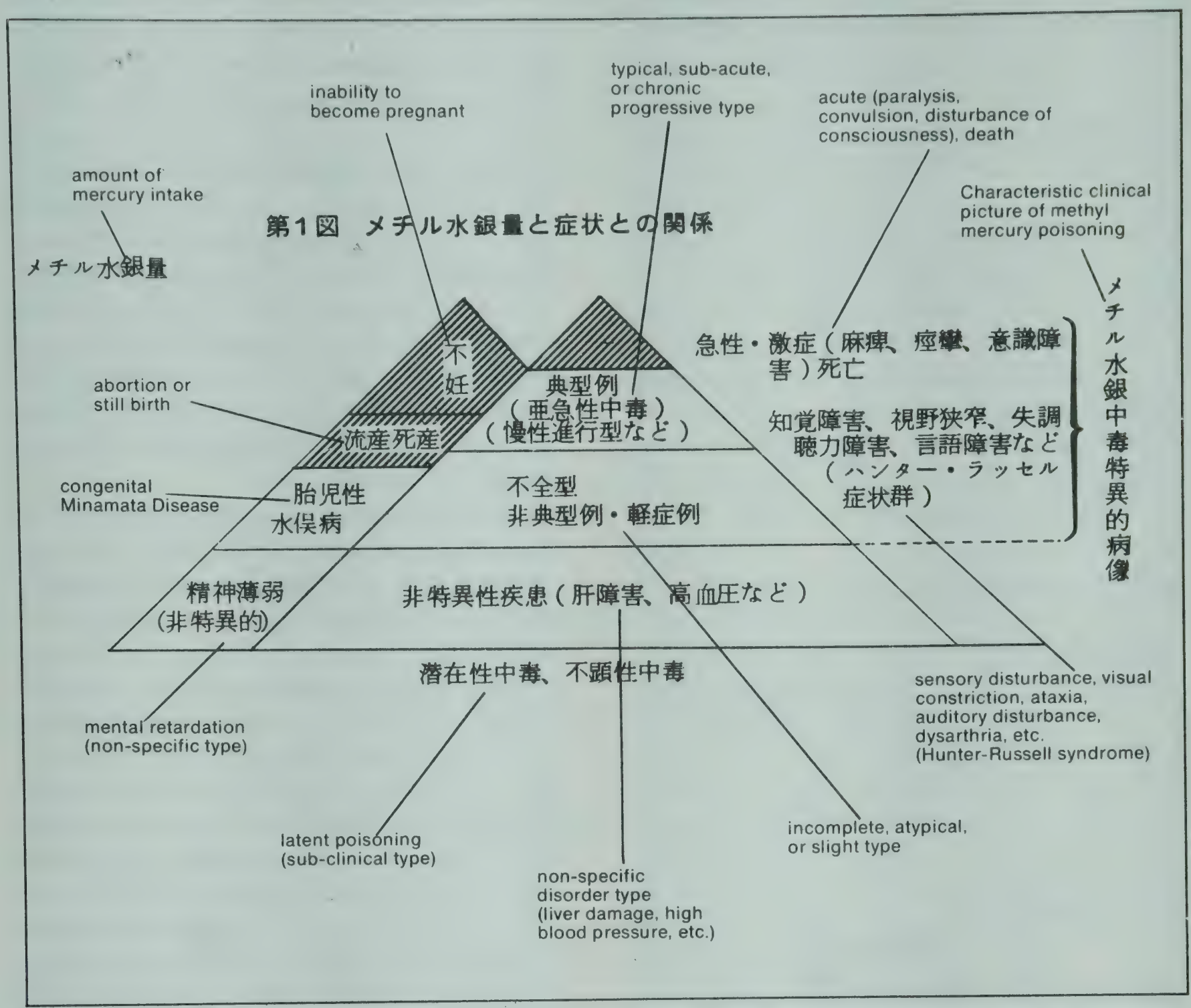
The present "safety" level of total mercury in fish is 0.4 ppm in the USA and Japan.[45]

Among Minamata Disease patients studied in the prefecture of Niigata, it has been calculated that an accumulation of 30 mg of methyl mercury in a 155-pound adult causes sensory disturbance, and that a 100 mg accumulation causes all the typical Minamata Disease symptoms found in the Hunter-Russell syndrome.

In Iraq, a 112-pound adult developed sensory disturbance after an accumulation of 25 mg of methyl mercury, disturbance of gait with 55 mg, dysarthria with 90 mg, auditory disturbance with 170 mg. A 200 mg accumulation caused death.[46]

When considering incomplete cases and

FIGURE 11 RELATIONSHIP OF METHYL MERCURY INTAKE AND SYMPTOMS



light cases, it can be calculated that an accumulation of over 25 mg is dangerous. On the basis of this calculation the oral intake and the rate of output are significant factors in measuring the total accumulation of mercury at a certain point.

Experimentally, the biological half-life of methyl mercury is calculated to be 70 days?[47] Since an accumulation in the brain is directly connected to the possibility of the appearance of symptoms, the half-life of methyl mercury in the brain is more significant. It has been found that methyl mercury can easily enter the brain, and that it remains in the brain much longer than in other organs. Takeuchi has calculated from autopsy results that the biological half-life of methyl mercury in the brain is 230 days?[48] Despite his finding, the present "safety" level is calculated on the 70-day biological half-life.

The Minamata Disease patients used as the basis for the calculation of the safety standard were acute typical cases. The calculation ignored the chronic and atypical cases which have now been discovered in Minamata. The calculation also ignores the fetus' great susceptibility to mercury poisoning. It also does not fully consider the greater influence such poisoning may have on individuals with other complications.

When considering the safety level one must consider not the average but the exception. The safety level should be calculated to definitely avoid even the lightest of symptoms. It should be calculated to be safe for those consuming more than the average amount of fish and shellfish. For example, in Japan the Food Sanitation Research Division has estimated that the

average consumption of fish among Japanese fishermen is less than 200 grams per day. In Minamata the average consumption per day is 286 grams in winter and 410 grams during the summer.[49] Also, the calculation should consider the young and the weak as well as the healthy adult.

It must also be noted that there are no experiments as yet to prove how safe the presently calculated safety level is when amounts just on the so-called safe side are consumed continuously over a period of many years.

And finally, in this age of multiple pollutants in the environment, this safety standard has not considered the possibilities of multiple contamination: mercury from other sources and also the cumulative effects of other poisons in the environment.

Therefore, when these various factors are considered, it becomes clear that it is necessary to seriously re-examine the present approach in figuring a safety level.

No "Threshold Point"

The accepted concept of the safety level is based upon the idea that symptoms do not appear unless a certain amount of methyl mercury accumulates in the body. But it is misleading to think that therefore methyl mercury causes *no* cell damage until it reaches a certain level. Although outward symptoms may not appear until a certain level is reached, it can be assumed that damage is proportionate, to some extent, to the amount of mercury that is consumed and that passes through the body, whether or not the body's mercury content reaches a "dangerous" level at any given moment.

If so, there is no actual "safety level." The greater the methyl mercury intake, the greater the cell damage. The lower the intake, the less damage to cells. On the cellular level there is no "threshold point."

In fact, in Minamata and the surrounding area, symptoms are becoming evident for the first time in some individuals, even though at present most of the fish and shellfish in this area show a relatively low mercury content;[50] and persons showing symptoms have low levels of mercury in their hair.[51] This phenomenon cannot be explained by the mercury "accumulation theory" based on the concept of biological half-life.

There are three plausible explanations for the fact that the symptoms are showing up now:

1. The high level of mercury intake during the period before and after 1956 might now be causing the symptoms.
2. The brain damage already caused by methyl mercury during the period of greatest contamination might now be coming to the surface with aging or other factors.
3. In Minamata the inhabitants continued to eat fish which contained a relatively smaller amount of mercury: Long-term low-level consumption might be causing damage.

At this point it is impossible to state which of these three factors is most responsible for the present appearance of symptoms. Further investigation of the toxicity of methyl mercury should certainly pursue this issue.

Summary

In looking back at the history of medical research of Minamata Disease, one is astounded by the areas of research as yet untapped.

What we must do is to put to use the lesson of Minamata for the rest of humankind. There is no other way but to make the results of this massive human experiment completely clear.

Medically, that is the only way to compensate those already victimized.

We are grateful to Dr. Sanford Rothenberg for his generous assistance in preparing the English version of this report.

Footnotes

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50 (1973) Minamata Bay shellfish: maximum 3.5 ppm, minimum 0.01 ppm, average 0.47 ppm.

51 (1973) Maximum 14.8 ppm, minimum 2.14 ppm, average 6.16 ppm.

Bulletin of the Institute of Constitutional Medicine, Kumamoto University,
Suppl. 25; 1–60p. (1976)

INTRAUTERINE POISONING

Clinical and Epidemiological Studies and Significance of the Problem

I. PREFACE

In 1955, many cases of severe neurological disease were found in the Minamata area of Kyushu, Japan. In 1959 it was demonstrated that the symptoms were due to intoxication by methyl mercury in effluent from an acetaldehyde plant of the Chisso Corporation. The toxin was transmitted through ingestion of seafood taken in Minamata Bay, hence the term "Minamata disease". (Study Group of Minamata Disease, Kumamoto Univ., 1966)

Meanwhile, in 1958, Prof. Kitamura had discovered that in the district there were many infants, born after 1955, who showed symptoms resembling those of cerebral palsy. He stated: "It is possible that the substance causing the poisoning was transferred to the infants through the placenta or mother's milk, producing symptoms similar to those of Minamata disease. But in every case the mother was healthy, and it was not until more than three months after birth that the symptoms were recognized, so the illness cannot be called Minamata disease conclusively at present." (Kitamura, S., 1959, 1960) These brief sentences comprise the essential problems of congenital Minamata disease.

Thereafter, careful epidemiological and clinical studies were conducted (Harada, M.; 1964, Harada, Y.; 1966), and pathological research as well (Takeuchi, T.; 1964, Matsumoto, H. et al; 1965), so that by 1962 the disease was identified as methyl mercury poisoning via placenta. Subsequetly, experimental findings confirming the fact have been made public successively (Morikawa, N.; 1961, Moriyama, H.; 1967, Fujita, E.; 1969). A long time was needed for reaching that conclusion because it was contrary to prevailing beliefs. It was thought that, as in the case of the blood-brain barrier, poison could not easily pass through the placenta, and that the fetus was thus protected. Actually, some poisons not only pass through the placenta but can also afflict the fetus without causing serious damage to the mother.

The incidence of such transplacental illness is by no means piculiar to Minamata. The problem of congenital diseases caused by environmental pollution is quite serious and it must be recognized as a universal one for mankind. All kinds of poison must be studied individually so that repetitions of the Minamata tragedy may be avoided. In cases

suggesting cerebral palsy or mental retardation, the possibility of such poisoning should be considered.

Congenital Minamata disease was first elucidated clinically in Minamata, but there have been some similar reports. Cases of cerebral palsy with mental deficiency are described in a report concerning poisoning caused by eating seed grain treated with alkyl mercury, announced in Sweden by G. Engleson et al in 1952. They suspected in this case that alkyl mercury had passed through the placenta. Perhaps this was the first description of what is now known as congenital Minamata disease. Reported thereafter were many cases in Minamata, one in Niigata, Japan; one in New Mexico (Snyder, R. D.; 1971); and 15 cases in Iraq (Amin-Zaki, L. et al; 1974). Judging from these facts, congenital Minamata disease is not the problem of Minamata alone.

The author has examined a great number of congenital Minamata disease patients and is reporting the most recent clinical as well as epidemiological observations. Much more observation and research is needed. Nevertheless, existing reports should now be made public in consideration of the controversy over environmental pollution, which will affect the next generation; these reports will contribute also to our understanding of the genesis and mechanisms of cerebral palsy, mental retardation and minimal cerebral dysfunction, for congenital Minamata disease seems to offer a model of these disorders.

II. INTRAUTERINE METHYL MERCURY POISONING IN THE MINAMATA AREA——CONGENITAL MINAMATA DISEASE

A. Epidemiological background

1. Morbidity: In the area where most Minamata disease cases are found——the three districts of Tsukinoura, Yudo and Modo——there were 220 births between 1953 through 1955. By the time of the first survey, conducted in 1962, thirteen serious cases of cerebral palsy were found in these districts. The incidence rate of such cerebral palsy was 6.9%. However, a later survey conducted on all the infants living in these districts revealed three children with mental deficiency and relatively mild neurological symptoms, and it was discovered that one other patient had moved to another district. Taking these cases into account, the morbidity is 7.7% (Harada, M.; 1964). There is a report that in other districts of Japan the morbidity for cerebral palsy in children 5 to 15 years of age ranges from 0.2–2.3 per 1,000 to a peak of 5 per 1,000 (Fukuyama, Y.; 1971). Compared with these figures, the incidence rate in the Minamata area during that period was abnormally high.

2. Areas of incidence: At first many congenital Minamata disease patients were found in fishing villases around Minamata Bay (Fig. 1).

Incidence areas and the incidence period (Fig. 1,3) coincided completely with outbreaks of acute severe Minamata disease among adults (Fig. 2,3). These epidemiological findings have been used to postulate that the cases called "cerebral palsy" were actually congenital Minamata disease. But the periods as well as the areas of incidence have been revised greatly by researchers since then. Up to the present, 40 congenital patients have been confirmed in the Sea of Shiranui area (Fig. 4). There is a strong possibility that such "hidden" cases will be found in the future. For example, on Amakusa and Shishijima islands, across from Minamata, the typical syndrome of madness and death of

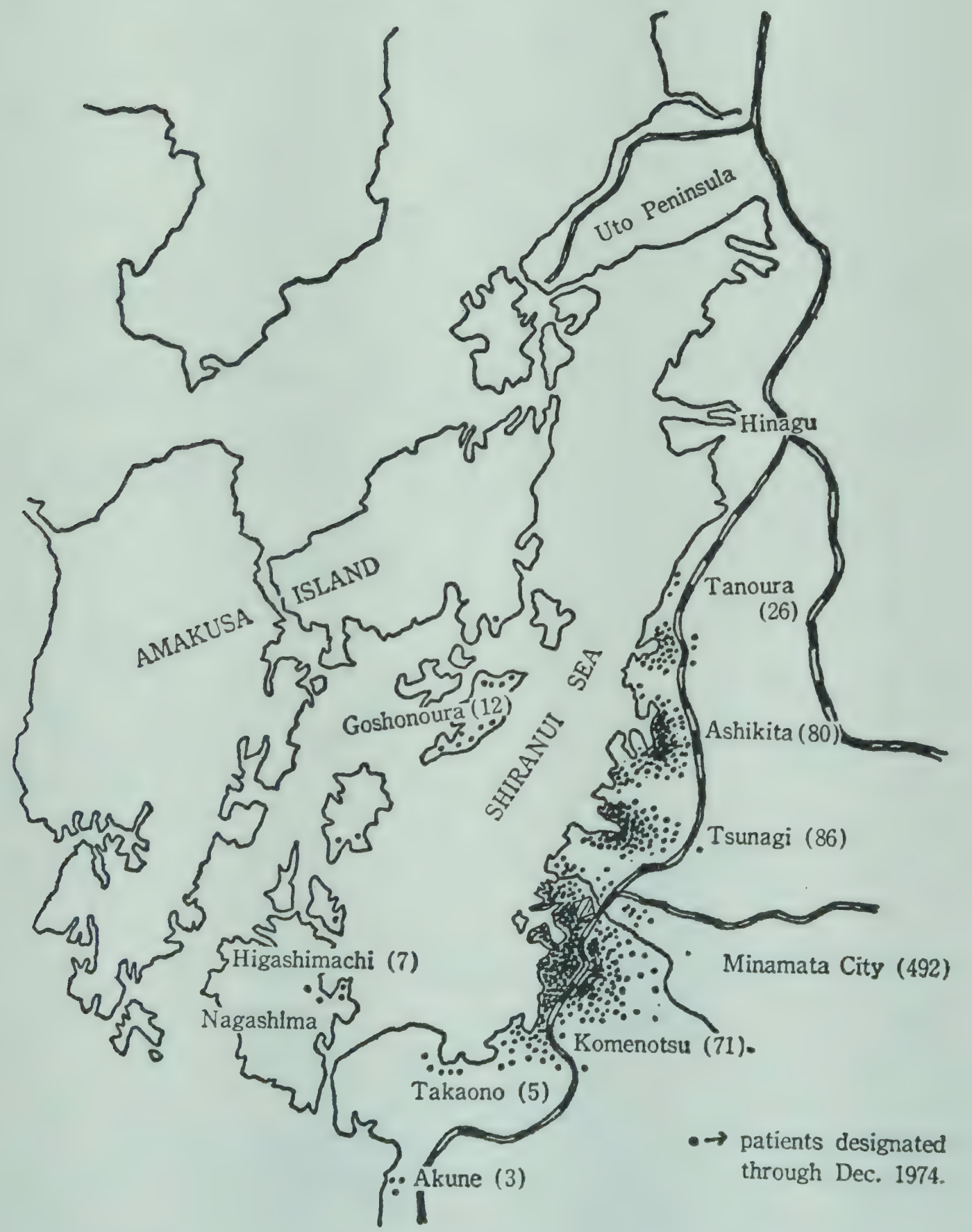
Fig. 1: Distribution of Congenital Minamata Disease in 1962. (M. HARADA)

Many cases of congenital idiocy accompanied by various neurological symptoms had broken out on the coast of Minamata city during the same period as the outbreak of Minamata disease.

cats has been seen, and adult patients have been found recently. However, congenital Minamata disease has not yet surfaced.

3. Minamata disease among family members: Of the congenital Minamata disease patients, 64% were living in families among whose members there were acute Minamata disease patients (Harada, M.; 1964). A survey conducted in 1972 revealed symptoms thought to be caused by methyl mercury in families of all the congenital patients. The symptoms of family members ranged from mild to severe. It is notable that symptoms of the mothers were relatively mild (Harada,

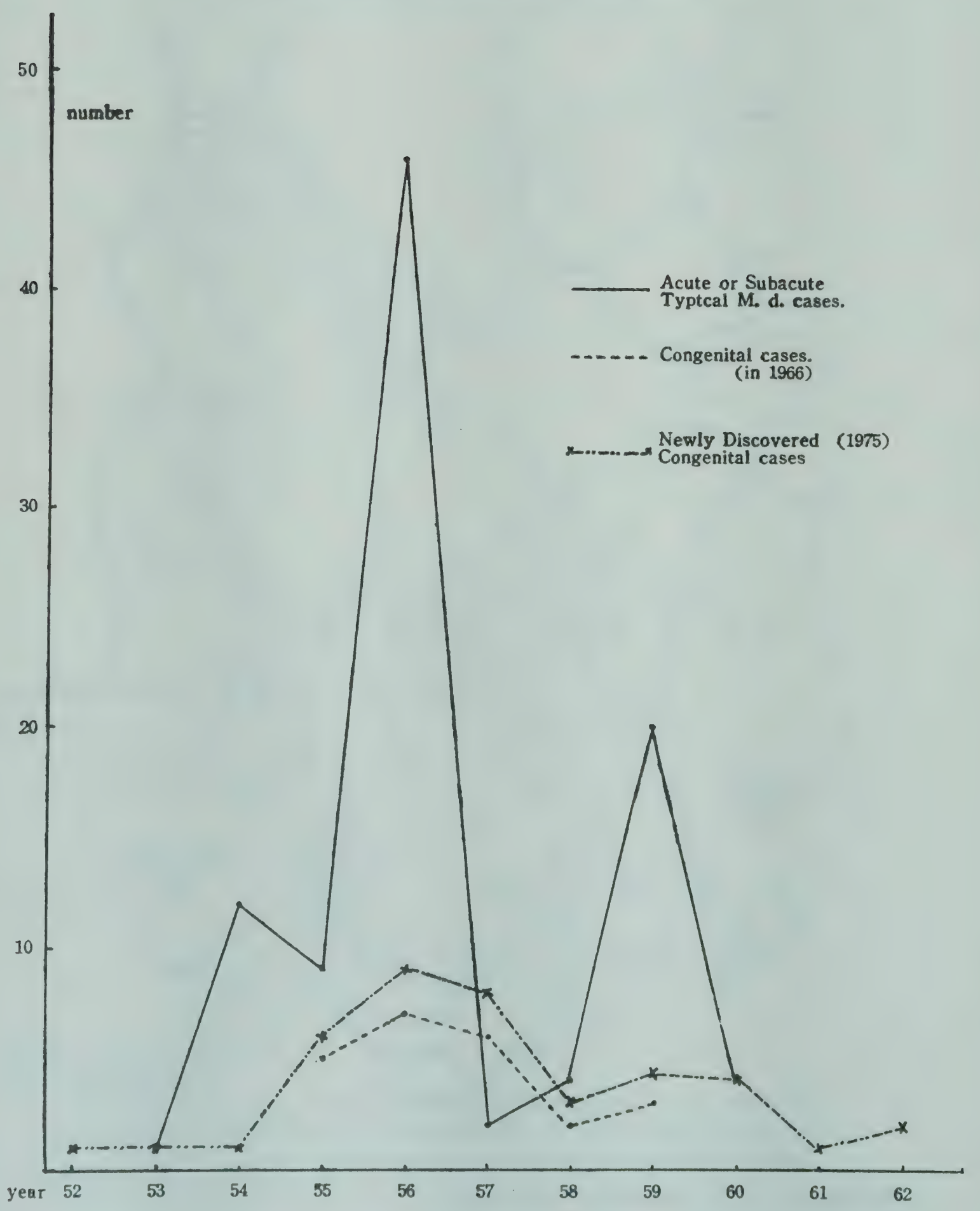
Fig. 2: Distribution of Officially Designated Minamata Disease Patients.



Figures in ( ): number of patients

M.; 1972, 1974). In 1962 the author et al recognized mild symptoms of Minamata disease in 11 out of 15 mothers of congenital patients. A followup survey showed that in all these cases the condition of the mothers had deteriorated, and neurological symptoms of some kind were recognized (Table 1). But again, symptoms of the mothers were mild. Also, among congenital Minamata disease patients, it was found in five cases that brothers or sisters of the patients had been afflicted with acute Minamata disease in their childhood. In each of two families, two brothers were suffering from congenital Minamata disease

Fig. 3: Comparison of Annual Incidence of Minamata Disease Case (Designated) Through 1971.



(cases mentioned later).

4. Mercury concentration in the hair: In the early period following discovery of the disease, the cause was not known. Therefore, mercury concentration in the body at that stage, the most important one, was not recorded. It was in 1960 that mercury concentration in the hair of Minamata disease patients was measured for the first time. At that time the age of congenital Minamata disease patients ranged from 13 months to 4 years and 4 months. Still, mercury concentration in the

Fig. 4: New Distribution of Congenital Minamata Disease Patients.(1975, Harada, M.)

Table 1. Clinical Symptoms of Mothers of Congenital Minamata Disease Patients.

(1974, Harada, M.)

Symptoms	Number	%
Sensory disturbance	28	100
Constriction of visual fields	16	57
Dysarthria	12	43
Incoordination (Total)	22	79
Ataxic gait	12	43
Finger-finger test	16	57
Adiadochokinesis	22	79
Auditory disturbance	21	75
Tremor	11	39
Muscular rigidity & spasticity	10	35
Hyperreflexes	11	39
Pathologic reflexes	3	11
Deformities of limbs	4	14
Pain	18	64
Disturbance on intelligence	20	71

Table 2. Mercury Concentration in the Hair of Infants.

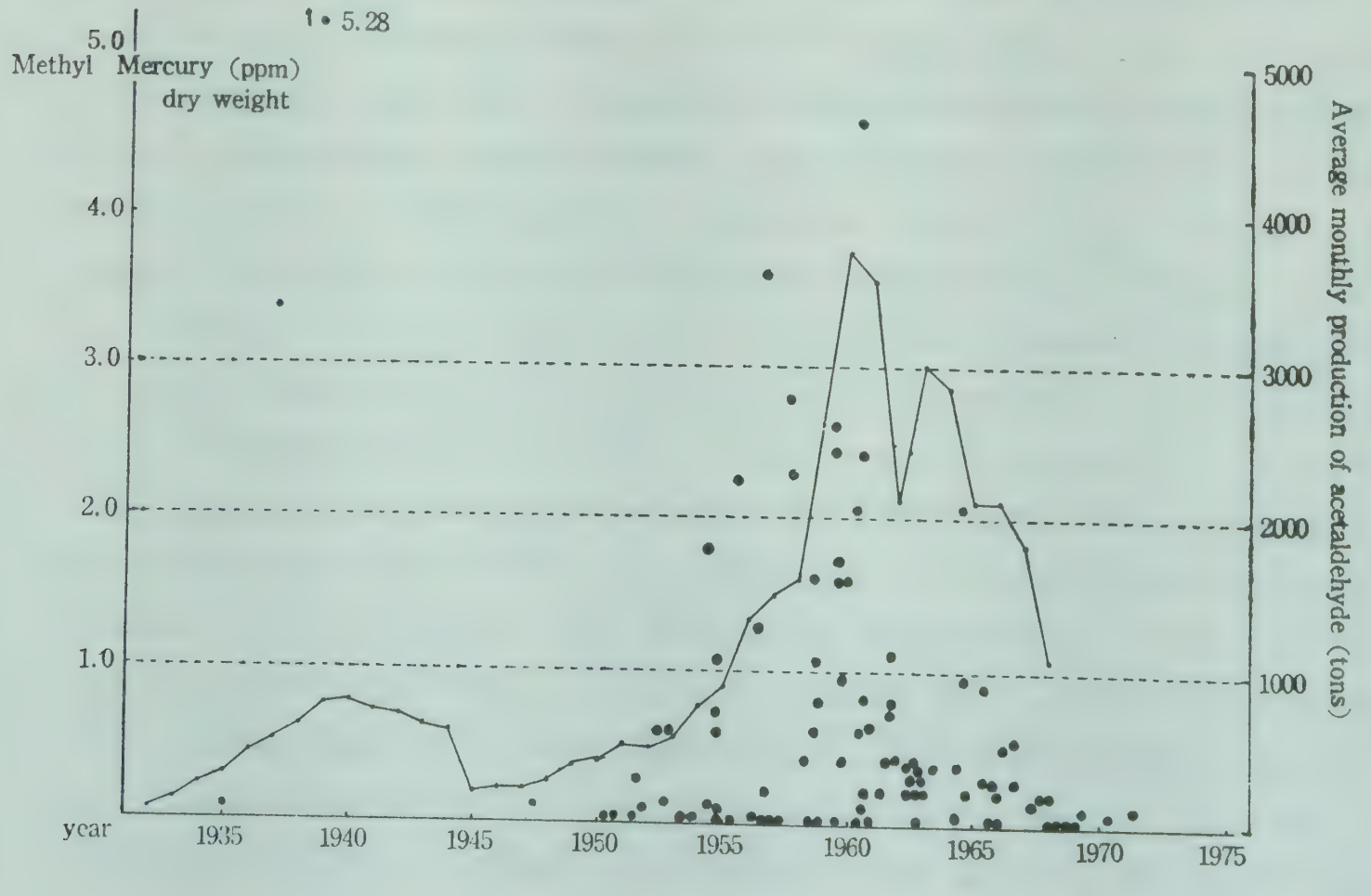
Minamata Area (Modo, Yudo & Tsukinoura)					Kumamoto City			
Congenital cases		Mothers of patients	Healthy infants		Healthy infants		Cerebral palsy	
Age: month	Hg Value (ppm)	Hg Value (ppm)	Age: month	Hg Value (ppm)	Age: month	Hg Value (ppm)	Age: month	Hg Value (ppm)
3:5	59.0	72.9	3:0	11.5	1:11	2.81	1:3	1.65
2:10	34.3	65.4	3:0	48.4	3:9	2.30	1:4	2.01
2:7	61.9	101.0	2:0	4.16	4:4	7.49	1:5	1.42
2:7	92.0	—	3:0	13.0	4:4	0.64	1:6	2.10
2:7	0	—	4:0	61.0	4:5	2.86	1:6	7.65
3:7	57.8	191.0			4:8	2.15	1:10	3.04
2:1	37.7						2:10	1.42
3:5	26.2	—					2:4	1.30
1:3	35.0	—						
1:1	5.25	6.56						
4:4	11.3	12.7						
3:8	10.0	1.82						
3:6	100.0	—						
4:1	73.5	90.0						
4:3		16.0						

(measured by Kitamura, S. in 1960)

hair showed high values (Kitamura, S.; 1966). While controls in Kumamoto City showed mercury concentrations of 1.30 to 7.67 ppm, congenital Minamata disease patients showed a maximum of 100 ppm (Table 2). Also, the mothers of congenital patients showed high mercury concentration in the hair (Harada, Y.; 1966). Meanwhile, in the Minamata area, mercury concentration in the hair of children without any serious neurological or mental symptoms was higher than that found in the control area. Therefore, in this stage of research, mercury concentration in the hair was thought to be a decisive factor for diagnosis. But in reality, it signifies only that Minamata was a heavily polluted area in which nearly everyone was contaminated.

5. Mercury concentration in the umbilical cord: Until 1960 the precise mercury value in the hair, blood and umbilical cord at birth was not determined. In 1960 to 1961, Prof. Y. Harada measured the mercury concentration in blood of umbilical cords of 7 newborns in Minamata area, showed mercury concentration of 0.24 to 1.46 ppm. In later years the author discovered that the umbilical cords of newborns were dried and preserved according to an old custom of Minamata and other regions. The author collected some of those umbilical cords and measured the mercury concentration in them. Because of the possibility that mercurochrome had been used in some cases, methyl mercury was measured instead of total mercury. Consequently, it has become clear that methyl mercury in the umbilical cords of inhabitants born in this area reflected pollution of the environment (Fig. 5). Moreover, the cords from congenital Minamata disease patients showed

Fig. 5: Methyl Mercury in Umbilical Cords Preserved in Minamata Area.
(Harada, M., Fujiki, M., & Nishigaki, S.)



relatively high methyl mercury values (Harada, M.; 1975).

In some cases the cords showed high values although the respective subjects were not considered to be suffering from congenital Minamata disease (examples mentioned later); and there were other cases showing conspicuous neurological symptoms although the umbilical mercury value was low. One explanation of his discordance is that the methyl mercury value in the dried umbilical cord shows the degree of contamination at a certain time but not during the whole prenatal period. Perhaps the sampling included some cases of cerebral palsy due to other factors but indistinguishable from the mercury-related disorder clinically or epidemiologically; however, the number of such cases probably would be small.

6. Prenatal and perinatal period: In the majority of congenital patients, no abnormality capable of causing brain injury was observed during pregnancy or at delivery. Body weight at birth was nearly normal except in two cases, in which weights were 2,000 g and 2,750 g. All except one newborn were full-term, and none of the mothers noticed abnormalities immediately after delivery. Of the sampling, 30 infants were breast fed, 6 had mixed feeding, and 4 were given artificial feeding.

B. Case histories

Case 1. Female, born on May 15, 1956. Parents' occupation, fishing. The sixth of seven children. The fifth, a boy, died of acute Minamata disease at the age of 4. The seventh child suffered from congenital Minamata disease. Subject was born when the mother was 41 years old. Normal delivery, weight 3 kg, breast fed.

Three months after birth, she was found to be unresponsive to light. At 18 months, general convulsion was observed. Thereafter, she was devoid of spontaneous movement and speech. At the age of five, (author's first examination; 1961) height was 81 cm, weight 8.5 kg. Did not speak at all, and was in the condition of akinetic mutism. There was slow and slight athetosis of the head, lips and tongue only. Drinking and eating were badly impaired, and the mother put soft food into her mouth bit by bit. Expressions of mental states, such as laughing or crying, were absent. There was no response to outside stimulation, and even if a fly landed on the eye she did not blink. Distortions of posture were conspicuous. She turned the head backward, rotating it to the left, and always slept on the left side, flattening the skull on that side. She was microcephalic, and deformities of the limbs were conspicuous (Fig. 6). The neck was weak and it was difficult to sit her up. In the eyes, spontaneous nystagmus was seen. Left and right eyeballs moved separately and slowly. Pupillary reaction was

Fig. 6: Deformities of Limbs, Nutritional Deficiency, Stunted Growth, Akinetic Mutism.

Female aged 6 years (Case 1), Died in 1962.
(Photographed by Harada, M. in 1962.)

normal. Muscular tone was strongly rigid, and muscle-stretch reflexes all hyperactive. Pathologic reflexes such as Babinski's sign, Rossolimo's sign, Oppenheim's sign, Hoffmann's sign, patellar clonus, foot clonus etc were all present. Primitive reflexes, general convulsion, hypersalivation and difficulty of swallowing were observed also. Patient died on September 12, 1962. Autopsy was performed five hours after death by Prof. Takeuchi (Takeuchi, T.; 1965). Pathological examinations revealed condition characteristic of Minamata disease, and impaired development of the brain during the prenatal period.

Prof. Takeuchi reported the following pathological diagnosis:

1) Fetal Minamata Disease
   a) Bilateral cerebral atrophy and hypoplasia
      i) Decrease and disappearance of the cortical nerve cells
      ii) Hypoplasia and malformation of nerve cells
   b) Cerebellar atrophy hypoplasia
      i) Atrophy of the central and granular type cell
      ii) Hypoplasia of granular cell layer and other layers
   c) Abnormality of the cytoachitecture
      i) Remaining matrix cells
      ii) Intramedullary preservation of the nerve cells
   d) Hypoplasia of corpus callosum
   e) Dysmyelination of pyramidal tract
   f) Hydrocephalus
2) Malformation and emaciation of body and organs
3) Gastrointestinal catarrh
4) Hypoplasia of bone marrow

5) Bronchopneumonia
6) Bedsores at sacral region
7) Agonal intussusception of the small intestine

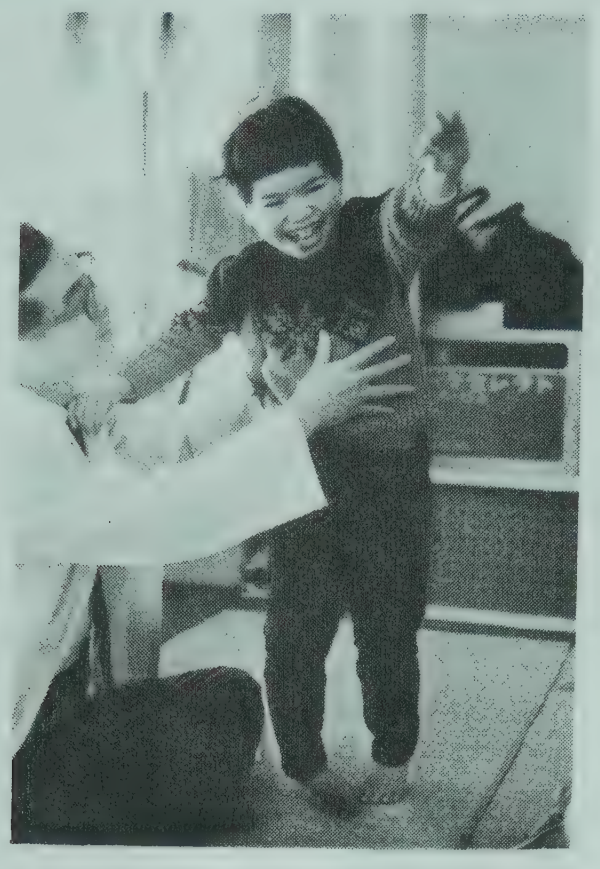
Case 2. Female, born on October 29, 1957. Younger sister of Case 1. The mother gave birth to her at the age of 42. Delivery was normal, weight at birth 3 kg, mixed feeding. Six months after birth the neck was unstable and the infant had no voice, so that the mother became aware of abnormality. At 4 years and 8 months (author's first examination), the neck was still unstable and the child was unable to sit up alone, stand up, or walk. She could sit up with aid, but without support from behind the upper half of the body was unstable and collapsed. When she tried to move forward on all fours, her body was still unstable, her arms and legs did not advance alternately, her forehead touched the floor and she fell down. When called by her name she responded, saying "haaai" (yes) slowly and drawlingly, but no other words were uttered. The mouth was half open, lips were slack and the child showed little interest in anything. At that time, height was 88 cm, weight 9.5 kg. Deformities of lower limbs were conspicuous. Being hypotonic, when she was laid on the bed she did not move at all. Athetosis of fingers and chorea of the neck were observed. Strabismus, nystagmus and difficulty in swallowing were also seen. There were primitive reflexes of the limbs, muscle tone was hypotonic-spastic, muscle-stretch reflexes were hyperactive; also, Babinski's sign and Rossolimo's sign were recognized. Hypersalivation was conspicuous. General convulsions instigated by fright or hunger were observed four or five times a month.

Later the patient was hospitalized for rehabilitation. At present (Dec. 1975), she can maintain a sitting posture. She can advance five or six steps on her knees, but walking is impossible. Since she has become able to respond to tests, adiadochokinesia, dysmetry and gross tremor on voluntary movement were confirmed (Fig 7). Her intelligence has developed and she can utter greetings or a few words of conversation. Speech is not clear, with stuttering and drawling. She has become able to tell her age, shows interest in television, and knows the program in which her favorite singers appear. She can indicate parts of the body almost correctly but cannot distinguish left from right.

Even with use of the fingers she cannot count to ten. She expresses likes and dislikes and has become able to express her intentions, but she still must wear diapers.

The mercury concentration in the mother's hair was 191.0 ppm in 1960; that of **Case 1** was 57.8 ppm, and of **Caes 2**, 37.7 ppm. Dysarthria, tremor and sensory disturbance are observed in the mother

Fig. 7: Unable to stand up alone, Ataxia, Hypersalivation, Dysarthria, Mental Retardation.



Female aged 4 years (Case 2).

herself, but she does not need help in her daily life.

C. Clinical symptoms

About six months after giving birth the mothers began to notice their babies had difficulty in holding up their heads. In some cases, tonic convulsion, failure of the eyes to follow, or weak response, attracted the mothers' attention to the abnormality of the infants.

Clinical symptoms are both neurological and mental. They are varied, but patients show very similar clinical pictures (Fig. 8). It was reported in 1962 by the author that mental retardation, cerebellar symptoms, dysarthria, extrapyramidal and pyramidal symptoms, paroxysmal symptoms, strabismus, hypersalivation, deformities of limbs and malnutrition were especially conspicuous (Table 3). (Harada, M.; 1962) In a survey conducted later, similar syndromes were frequently observed in recently found new patients (Harada, M.; 1974).

1) Disturbances on intelligence: Such conditions are observed in all the cases. In especially severe cases, akinetic mutism is observed (Fig. 6), and the intelligence of many patients is at the idiot level. In serious cases, forced laughter and forced crying are observed (Fig. 9). In mild cases, intellectual functions are not disturbed to the same degree, but there are wide discrepancies among various functions—— i. e. defficulties in calculation, reading and writing are quite serious, but impairment of judgement and thought is relatively mild.

2) Personality disorders: Commonly observed are such characteristics as unfriendliness, apathy, abnormal shyness, irritability, sulleness,

Fig. 8: Congenital Minamata Disease Patients in Minamata Area.

The patients showed very similar clinical picture each other.
(Photographed by Harada, M. in 1962.)

Table. 3 Frequency of Symptoms in Congenital Minamata Disease

	1962		1971		1974	
	cases	%	cases	%	cases	%
Mental retardation	17	100	25	100	37	100
Dysarthria	17	100	24	96	34	92
Extrapyramidal hyperkinesia	16	95	23	92	34	92
Cerebellar symptom	17	100	19	76	29	78
Deformities of limbs	17	100	21	84	23	62
Primitive reflexes	17	100	18	72	25	67
Strabismus	13	77	18	72	25	67
Hypersalivation	17	100	18	72	27	72
Paroxysmal symptom	14	82	9	36	13	35
Pathological reflex	12	75	12	48	17	45
Inhibited bodily growth	17	100	17	68	22	59
Number of cases	17	—	25	—	37*	—

* Based on a total of 40 cases of congenital M. d. of which, 3 died.

(Harada, M.; 1974)

Fig. 9: Forced Laughter, Similar Condition of Akinetic Mutism.

Female aged 5 years.

stubbornness, restlessness, hyperkinesia, fearfulness, and abnormal propensity to laugh or cry.

3) Primitive reflexes: In serious cases, such primitive reflexes as grasping, opening the mouth and sucking are observed.

4) Hypokinesia, hyperkinesia and disturbance of muscle tone: In hypokinesia and hyperkinesia, mental and extrapyramidal symptoms are mingled. Chorea and athetosis are also seen. Rigidity and spasticity

often coexist.

5) Cerebellar symptoms: It is impossible for such patients to maintain the head in an erect position, and the whole musculature becomes flabby (hypotonic). Ataxia renders the patients unable to hold a sitting position (Fig. 10, 11), and disturbances in gait are observed (Fig. 12). Also observed are such symptoms as dysarthria, gross tremor during voluntary movements, nystagmus, adiadochokinesia, hypermetry and dysmetry. In mild cases, or when symptoms improve, cerebellar symptoms become recognizable.

6) Paroxysmal symptoms: Tonic convulsion is most frequent, and

Fig. 10: The Nock is unsteady, unable to sit up.

Male aged 6 years.
Born in 1956, symptoms did not improved at all, died in 1968.

Fig. 11: Unable to sit up. Ataxia.

As someone tries to sit up her up, she raises arms, trying to keep balance. Female aged 5 years.

Fig. 12: Ataxic Gait, Dysarthria and Strabismus. Light Case.

Female aged 5 years.

myoclonic jerk, grand mal, and loss of consciousness are observed also. Paroxysmal symptoms are among those that disappear easily. Also, epileptic abnormality is often observed in the EEG. In 1962 the author recognized paroxysmal discharge in the EEG of 6 cases out of 14 (Harada, M.; 1971); in 1966, Y. Harada made the same finding in 6 cases out of 19 (Harada, Y.; 1966).

7) Strabismus and hypersalivation: These symptoms are quite frequently observed.

8) Pyramidal symptoms: Compared with Minamata disease in adults, the rate of pathologic reflexes is high. However, differences between right and left sides are not noticeable.

9) Deformities and posture: Abnormalities of posture caused by deficiency in muscle tone can be observed. The degree of deformity of fingers can be observed (Fig. 13). Compared with other symptoms, malformation is relatively mild. There is one case of malformation of the auricle and acoustic meatus, and six cases of microcephaly, but features of the face are regular.

10) Growth and nutrition: Deficiencies in growth and nutrition were observed in all cases in the early period, but there has been gradual improvement. In serious cases both height and weight were astonishingly low. One patient, aged 18, weights 18 kg and stands 109 cm. One of the reasons for malnutrition is motor dysfunction such as disturbances of ingestion, mastication and swallowing. However,

Fig. 13: Deformities of Fingers and Changes in Nails.

disorders of the central nervous system and endocrine glands are related.

11) Sensory disturbances: In 1960, visual disorder was suspected in six cases. Visual power became affected gradually and four cases of visual disturbance were suspected in 1962. The escaping reaction in response to stimulation can be observed, but details of superficial sensory disturbance are unknown. In mild cases, disturbances of peripheral nerves have not been confirmed. In the early stage it was impossible to test for constriction of visual fields, but in 1973 four cases were confirmed among mildly affected patients (Harada, Y.; 1973). Also, author confirmed this in 1974 (Fig. 14). Auditory disturbance cannot be tested with any precision; one patient is a complete deaf-mute.

12) Comparison with exogenous idiocy or cerebral palsy in general: Congenital Minamata disease has many typical characteristics, clinically, but the same symptoms can be caused by factors other than methyl mercury. Congenital Minamata disease resembles exogenous idiocy, cerebral palsy, and other mental and physical handicaps, so its diagnosis is sometimes difficult. But if comparison is made in terms of groups, the characteristics of the disease become clearer (Table 4).

Compared with congenital Minamata disease patients as a group, victims of exogenous idiocy show cerebellar symptoms or strabismus less frequently; pyramidal symptoms, palsy, differences in left and right sides, and factors causing cerebral dysfunction, are observed more often. Mental retardation is milder in the cerebral palsy group, cerebellar symptoms are milder, and chorea and athetosis are conspicuous. Factors causing these disorders are often recognized (Harada, M.; 1962).

D. Course of clinical symptoms

In the earlier period, cases identified by the author were typical,

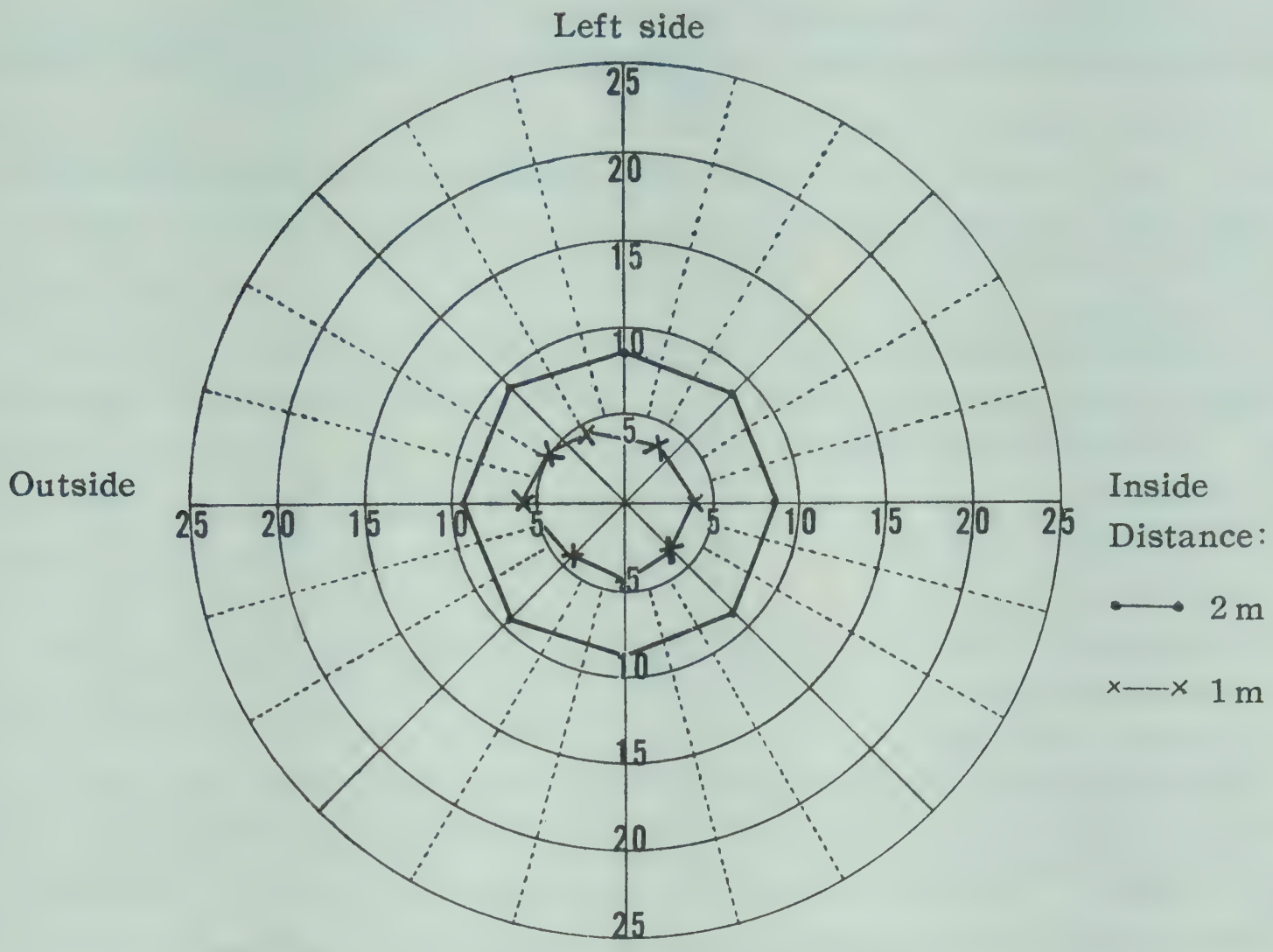


Fig. 14: Constriction of the Visual Field.
(Male, 17 years old of Congenital Case,
Measured by Prof. Tsutsui in 1974)

Table. 4 A Comparison of Clinical Symptoms in Congenital Minamata Disease, Exogenous Idiocy and Infantile Cerebral Palsy. (%)
—— Harada, M.; 1962.

	Cong. M. d.	Exog. Idiocy	Inf. C. p.
Mental retardation	100	100	75
(serious case)	(100)	(100)	(25)
Cerebellar symptoms	100	33	18
Primitive reflex	100	61	31
Hyperkinesia	95	32	68
Hypersalivation	95	32	68
Paroxysmal symptoms	82	16	0
Strabismus	77	11	37
Pyramidal symptoms	75	100	43
Dysarthria	100	—	—
Deformity of limbs	100	100	100
Inhibited bodily growth	100	72	31
Asymmetry of the symptom*	0	72	18
Verification of cause	0	56	62
numbers of subjects	17	18	16

* Differences in motor disturbances on left and right sides.

Table. 5 Changes in Symptoms and Clinical Types.

		1962 (17 cases)	1971 (15 cases) total of appearence	disappeared	improved
Clinical symptoms	Mental retardation	17(15)*	15	0	11
	Primitive reflex	17(15)	10	5	3
	Cerebellar symptom	15(15)	13	2	5
	Extrapyramidal hyperkinesia & hypokinesia	16(14)	14	0	9
	Dysarthria	17(15)	15	0	2
	Paroxysmal symptom	14(12)	4	8	2
	Strabismus	14(12)	12	0	5
	Pathological reflex	12(10)	7	3	3
	Hypersalivation	16(14)	12	2	6
	Deformity of limbs	17(15)	15	0	9
	Inhibited bodily growth	17(15)	11	4	7
Clinical types	Predominantly akinetic type	5		1	(2 died)
	Predominantly hyperkinetic type	1		3	
	Predominantly ataxic type	8		4	
	Predominantly intelligently disturbed type	3		7	

* In 1962, 17 patients were examined and were kept under observation up to the present. Two cases died and the remaining 15 cases have been reexamined.

severe cases complete with the now-familiar symptoms. Before the causes had been elucidated, it was natural that we should try to clarify the characteristics of the disease by grouping patients who had all the symptoms. In this way we were able to conclude that the patients were afflicted with the same disease, from the same cause.

But although the symptoms were alike at the beginning, they changed in the course of more than ten years. Some symptoms can be alleviated easily while others cannot, and the pattern of the disease, reflected in changing symptoms, is transformed (Table 5). Paroxysmal symptoms and primitive reflexes have disappeared, and cerebellar symptoms have been relieved, although there is still awkwardness or clumsiness in movement. Intelligence has developed in all cases. In milder cases, some patients have become aware of their deficiencies and have worried about them; they have the ability to criticize themselves, and at the same time they have become more warm-hearted, humane and considerate of others.

Symptoms most difficult to overcome are strabismus and dysarthria. When motor functions improve, mental retardation becomes the main

symptom, and in some milder cases it is then impossible to distinguish between congenital Minamata disease and mental deficiency caused by other factors. Also, changes in the clinical type can be observed in infantile Minamata patients who contracted the disease in early infancy. Thus, impaired intellingence should be considered as one clinical type of the disease.

During the past ten years, two patients seriously afflicted with congenital Minamata disease died. In medium to mild cases, rehabilitation is effective, and relief of symptoms has been observed. But from now on both mental and social training as well as assistance in adjusting to social life will be necessary.

E. Mental deficiency due to methyl mercury

1) Background

Although clinical distinctions are recognized in congenital Minamata disease, comprehensive judgement is necessary for diagnosis. If Minamata disease is thought of as mass poisoning of the entire population through environmental pollution, gradations from serious cases to apparently healthy people must be perceived as a continuous spectrum.

The most serious cases of embryonic poisoning result in miscarriage or stillbirth. In the Minamata area, stillbirths and miscarriages registered with the authorities numbered 90.5 out of 1,000 births in 1960, 90.9 in 1965, and 69.9 in 1970; but relevant data available to us at present are fragmentary, and actual conditions have not been clarified. We know, however, that sublethal poisoning of the fetus results in serious brain damage —— now called congenital Minamata disease. Furthermore, in mild cases there is a strong possibility of mental deficiency as the main symptom. Considering the fact that from 1950 through 1960 this area was heavily polluted by methyl mercury, between the seriously-ill congenital Minamata disease patients and healthy persons there must be many degree of illness according to individual differences or degrees of exposure to pollution.

Data on this subject are scarce. However, in 1962 the author and co-workers conducted a survey to test the assertion that the outbreak of congenital Minamata disease had occured only between 1955 and 1958. In testing 72 children born in 1953, 1954 and 1959 (before and after the period in question) we found that 29.1% of the sampling were mentally subnormal. Patients were evaluated in clinical examinations by neuropsychiatrists and by intelligence tests, in paper and those with IQ below 70 were classified as deficient (Harada, M.; 1962). The fact that such a high rate of mental retardation existed before and after the main outbreak of congenital Minamata disease suggests

that the situation is much more grave than had been imagined.

In 1971 the author and co-workers conducted a mass examination of mental and motor functions of school children born between April 1955 and March 1959 in the same area. Compared with schoolchildren of similar age in the control area, intelligence deficiency was found in 18% of the sampling (statistically significant difference $p<0.001$); sensory disturbance in 21% ($p<0.001$); and mild speech disorder in 12% ($p<0.001$). Adiadochokinesis (symptoms observed in so-called clumsy childen, e. g. inability to stand one foot) in 9% ($p<0.05$) was confirmed (Table 6). The incidence rate of mental deficiency in other

Table. 6 Frequency of Occurrence of Symptoms in Pupils of Lower Secondary School in Minamata Area. (13~16 years old)

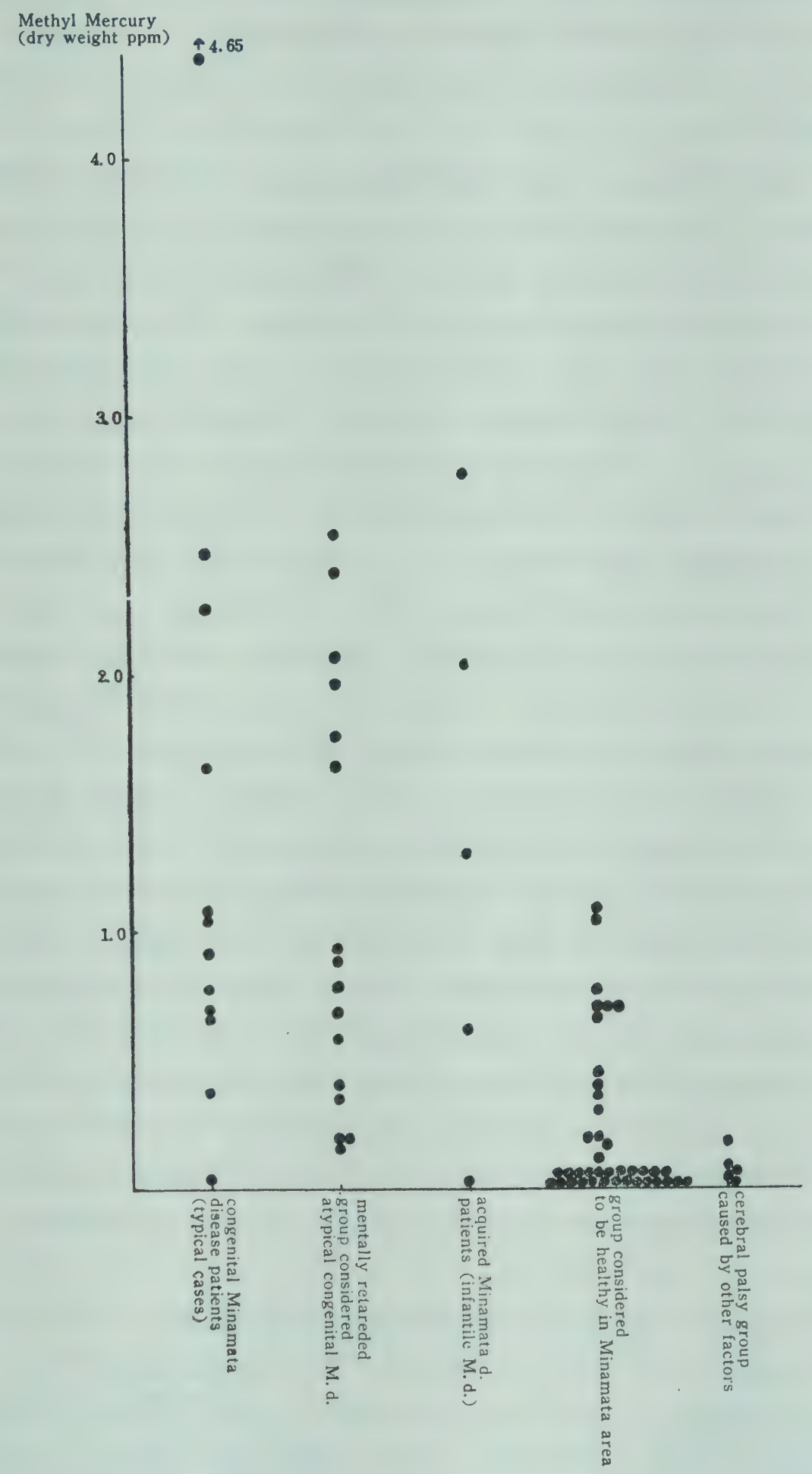
	Minamata area	Control
* Sensory disturbance	47(21)	5(3)
Auditory disturbance[1].	19(9)	19(10)
Strabismus	11(5)	10(5)
Nystagmus	11(5)	11(5)
* Adiadochokinesia	20(9)	8(4)
* Dysarthria	26(12)	4(2)
Pathological reflex	8(4)	6(3)
Constriction of the visual field[2].	2(1)	0(0)
* Mental retardation	39(18)	14(7)
Total	223(100)	196(100)

* means $p<0.01$
(Examined by M. Harada & T. Fujino in 1971)
1) Tuning fork was in auditory disturbance test.
2) Confrontation test was applied for constriction of the visual field.

parts of Japan, according to interviews by psychologists, is said to be 4.53% in primary schools and 7.2% in junior high schools, while the rate in the general population is 2 to 3%. Although the data are fragmentary, the author and his co-workers strongly suspect the results of surveys indicate prevalence of mental deficiency caused by methyl mercury.

As mentioned previously the author measured methyl mercury in the umbilical cord. Thereafter, the methyl mercury value and clinical symptoms were studied together. This comparison revealed exactly the same pattern as that observed in comparing the group of congenital Minamata disease patients and the group of mentally retarded children in Minamata area. More than 0.5 ppm of mercury was detected in many umbilical cords of congenital Minamata disease patients. Mercury value in umbilical cords was also high in a group of mentally retarded children, born in the Minamata area, whose neurological

Fig. 15: Clinical Symptoms and Mercury in Umbilical Cords
(Cases born between 1950 and 1965 were subjects in Minamata Area)



symptoms are not conspicuous. These cases were considered clinically to be suffering from in complete or atypical congenital Minamata disease. However, those who did not show symptoms showed high mercury value in the umbilical cords. Also interesting is that in several cases of apparently postnatal Minamata disease, the mercury value in umbilical cords was high. In continuous poisoning caused by environmental pollution, such as Minamata disease, there are some cases in which the fetus was contaminated by mercury in utero, and

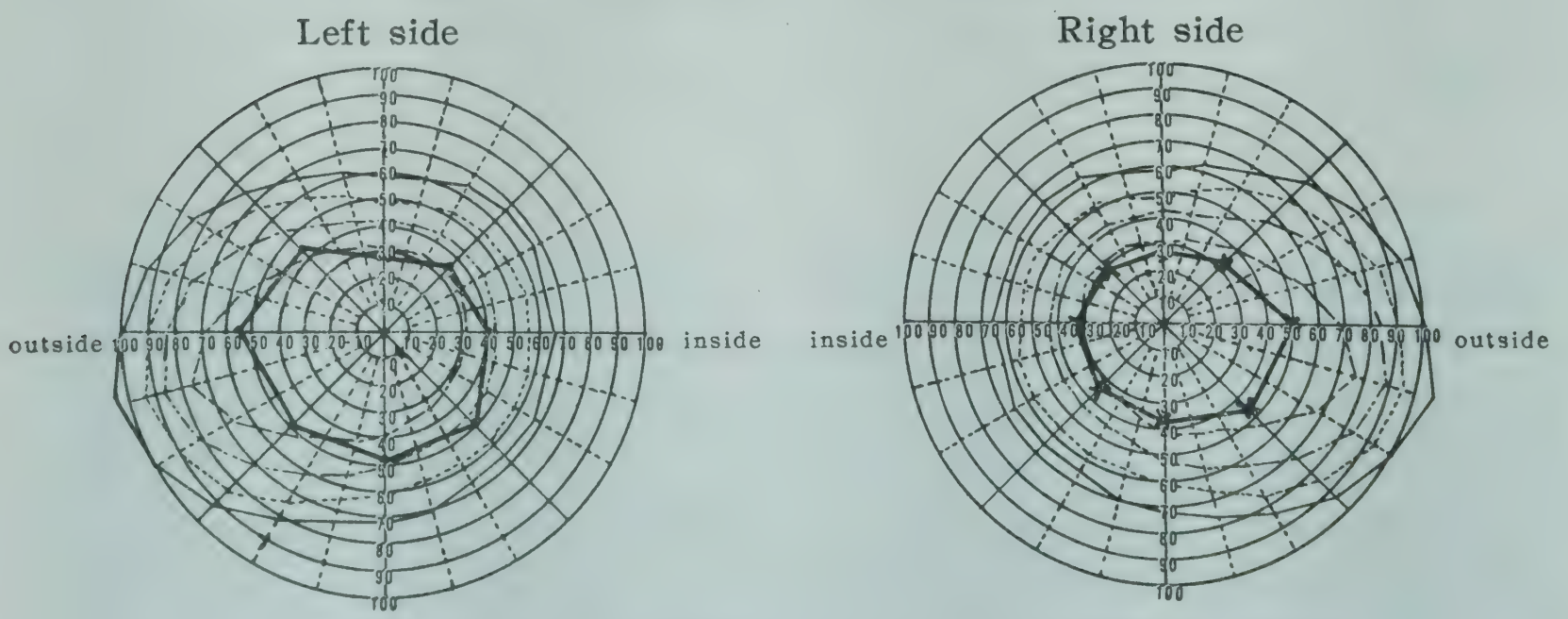
child suddenly contracted the disease by ingesting food highly contaminated with mercury later on. This fact indicates also that in Minamata area some of those diagnosed as mentally deficient might have been affected by methyl mercury (Fig. 15).

2) Case history

Case 1. I. H. Female, born on November 11, 1956 in Minamata City. The family ate fish about once every other day and the amount of it ingested was not unusually great. The family sometimes obtained very fresh ones from the fisherman S. in Modo. The patient's mother regularly purchased oysters, sea cucumbers, short-necked clams and other shellfish from a fish vendor, A, from Tsukinoura. Particularly during her pregnancy in 1956, she ate consiederable quantities of them. Incidentally, Modo was, in 1956, one of the villages most affected by Minamata disease, and fisherman S. as well as his wife suffered from the disease. Tsukinoura also was in the area most severely affected by Minamata disease, and A's parents and his younger brother were stricken by it. This brother of A had an onset of the disease in June, 1956, at the same time the patient in Case 1 was born.

Prenatal period and condition of her mother: The mother gave birth to her at the age of 31. The pregnancy and delivery were normal, weight at birth 3 kg, mixed feeding. After delivery, the mother experienced severe and general fatigue unlike that known previously she experienced frequent muscle twitch and cramps in the limbs. At one point, due to tremor and awkwardness of hand movement, her handwriting became clumsy but this condition later improved. According to the author's clinical examination in 1975, convergence disturbance, slight dysarthria (slowness of conversation), mild auditory disturbance, slight muscular rigidity, perioral and peripheral sensory

Fig. 16: Constriction of the Visual Field.



I. H. case's mother aged 30 years shows constriction of the visual field, sensory disturbances and mild incoordination.

disturbances and constriction of the visual field (Fig. 16) were observed. Ataxia is very mild, and she reveals a slightly swaying gait on a straight line. In the finger-nose test, the patient missed her nose by one to two cm. Diadochokinesia were clumsy. In the heel-knee test, the patient demonstrated awkwardness, missing her knee by about five centimeters and dropping her foot as if to bang it on the floor. Therefore, author considered her mother as a mild case of Minamata disease.

History: Six months after birth the infant demonstrated only very limited physical motility and responsiveness. An unstable neck and hypersalivation were noted. After one year the patient became able to sit up and crawl about to some extent. One year and four months after birth, the patient developed general convulsions. By that time, she had become quite responsive and was able to walk with an unsteady gait by holding on to surrounding objects. The patient, however, uttered no words. Although she tried to speak, she seemed unable to move her tongue. The patient's development of mental functions and mobility continued to be retarded, but at the age of 4 she became able to eat with a spoon, and at the age of 7 she could comprehend most of about what others were saying. Although her speech was inarticulate, her vocabulary increased. The patient, at the age of eight (in April, 1964), was enrolled in a special school.

Clinical symptoms at the age of 14 (March 26, 1970): The patient, overly shy and incooperative in the consultation, did not espond to examination in the beginning. Clinging to and playing with her mother, the patient was like a small child, crying out whenever she was unwillingly examined. On the other hand, she was apt to laugh at even trivial matters. The patient was well-nourished and normally developed, no deformity nor malformation. Unaided but clumsily the patient was able to do what she was told to do (standing up, sitting down, buttoning buttons, serving tea); she could also relieve herself unaided but would soil her underwear. Dressing and undressing were possible but because she grasped the clothing directly by the palms, the process was slow, and awkward. She walked with long, strides, fast but roughly, the body swaying, the hands swinging. Romberg's phenomena were negative. The finger-nose, finger-finger and heel-knee tests indicated accuracy but slowness. Choreiform hyperkinesia of limbs, tic-like hyperkinesia around the mouth, voluntary hyperkinetic-like movement, myoclonic muscle twitching, athetosis of fingers and the toes, and fibrillary twitching were observed. Dysarthria was so remarkable that the spoken words were unintelligible. Because of mental retardation, details concerning disturbances of the visual field as well as the gustatory, olfactory, auditory and superficial

sensations were unknown, but there was response to stimuli. Hypotonia and hyporeflexia were observed but no pathologic reflex. Mild hypersalivation and palmar hyperhydrosis were present. She could name articles of daily use correctly but was unable to distinguish between left and right, or name of the fingers and other parts of the body such as elbow or chin. She could write her name and the numbers from one to ten but failed to execute even one-figure calculations using her fingers. She could not tell us her address or her age. She could carry on a telegramlike conversation. She tried to keep as far away from us as possible and was abnormally bashful, but once she became familiar with us she went to the other extreme, being too friendly and rather a nuisance by continually offering us oranges, tea or a cushion.

By 1975, she had grown in physical stature and was able to go shopping at a store about a hundered meters away, but only to fetch one thing at a time. She also began washing and sewing clothes in a very awkward manner. She was still incapable of looking after defecation and menstruation adequentely. Neurological findings revealed no great changes. Clumsiness and awkwardness of motion were still very marked as before, with continual stumbling and falling down. She could not jump (lifting both legs off the ground) and showed great clumsiness in using scissors and tying strings. She spent the entire day scribbling or watching television but never going out. Her case was officially diagnosed as exogenous idiocy, but should be diagnosed as congenital Minamata disease. of the type in which disturbance of the intelligence predominates.

F. The diagnosis of congenital Minamata disease

As late as 1962, it was still extremely difficult to establish a diagnosis of congenital Minamata disease for each individual cases. Although the disease itself was characterized by the combination of its various symptoms, not every symptom was found to be typical of the disease. Because of this, only epidemiological findings and collective comprehensive considerations could establish a diagnosis. If the case was a simple, isolated one, the diagnosis would be difficult to make even if some specific findings were pointed out pathologically.

The following is a list of important factors for the diagnosis. Perinatal period: It is important to try to eliminate other causative factors. Asphyxial delivery and premature delivery, however, could be caused by mercury poisoning. Moreover, there is also a question of whether or not asphyxial delivery could cause cerebral damage. Therefore, these factors cannot be completely ruled out.

Course and disturbances of growth: In most cases, the head would

be unstable. The patient would be found abnormal because of convulsions, partial lack of response and limited physical movement. Then, disturbances of intellectual development and motor function would be observed. Except in a very serious cases, in which the patients would die from complications, the aftermentioned development process would progress gradually and generally. These disturbances, in general would not be aggravated. In a case where convulsive fits are frequent, these disturbances probably would be aggravated and progressive.

Clinical symptoms: In the early stage, it was characteristic that the degree of intelligence disturbances and motor dysfunction, especially cerebellar symptoms, ran parallel with each other. Mental retardation would be found in all cases and would always be serious. It would remain so even if other symptoms were relieved, and therefore would become a great obstacle in the path of social rehabilitation. Extrapyramidal hyperkinesia, cerebellar symptoms, hyperextension and other deformities of the fingers, primitive reflexes, strabismus, hypersalivation, and paroxysmal symptoms would be observed as the principal symptoms, but hemiplegia and spinal symptoms would not be observed. In a case where intelligence disturbance is improve, concentric constriction of the visual field would sometimes be observed, but this could not be seen as a decisive factor for making the diagnosis as in the case of peripheral sensory and auditory disturbances which are characteristic of adult Minamata disease, because testing them would usually be very difficult. Tests on oculomotor abnormality (EOG), however, seem to be comparatively effective for that purpose. Since cerebellar symptoms, primitive reflexes and paroxysmal symptoms are apt to be alleviated as time goes by, they would not tend to be pronounced in mild or prolonged cases. However, as dysarthria is one of the most troublesome symptoms to relieve and is very characteristic of the disease, it should stand out as quite significant. The patients show no marked facial deformities nor abnormal expressions and, in general, have regular features. Dental malformation is said to be suggestive in some cases.

Mercury content in umbilical cords and hair: If the disease is due to mercury poisoning, it is of utmost importance to demonstrate that the patient has been contaminated by it. Therefore, if a high level of mercury were to found in some part of the body, that could become a very helpful factor in proving the contamination. Nevertheless, it would merely be an index of transitory contamination. I and my fellow researchers measured the methyl mercury content in preserved umbilical cords, and have confirmed that high levels of methyl mercury existed in the umbilical cords of congenital Minamata disease patients.

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Bangalore - 560 001.

In some cases, however, the levels were low, on the other hand, in some cases the levels were high but the symptoms were not serious.

Symptoms of the mother and family members: If Minamata disease could be difined as a dietetic poisoning, symptoms of the mother and other family members would be of great significance. Nevertheless, the symptoms of the mothers of serious congenital Minamata disease patients have so far proved to be comparatively light. Basically, therefore, the symptoms of the mother should be considered as mild or incomplete. Since the fetus is more susceptible to methyl mercury than the adult, it would become necessary to study carefully the symptoms of the mother and other family members even where they don't show typical Minamata disease symptoms.

Relation with breast milk: Since methyl mercury poisoning through the breast milk has been experimentally proven (Deshimaru, M.; 1972), the relationship between the disease and breast feeding cannot be neglected. Cases of such nature could be aggravated after birth or could develop intelligence disturbance accompanied by no physical symptoms, but either way, clinical diagnosis of such poisoning would be difficult.

III. A CASE OF CONGENITAL MINAMATA DISEASE IN NIIGATA PREFECTURE —— SECOND MINAMATA DISEASE

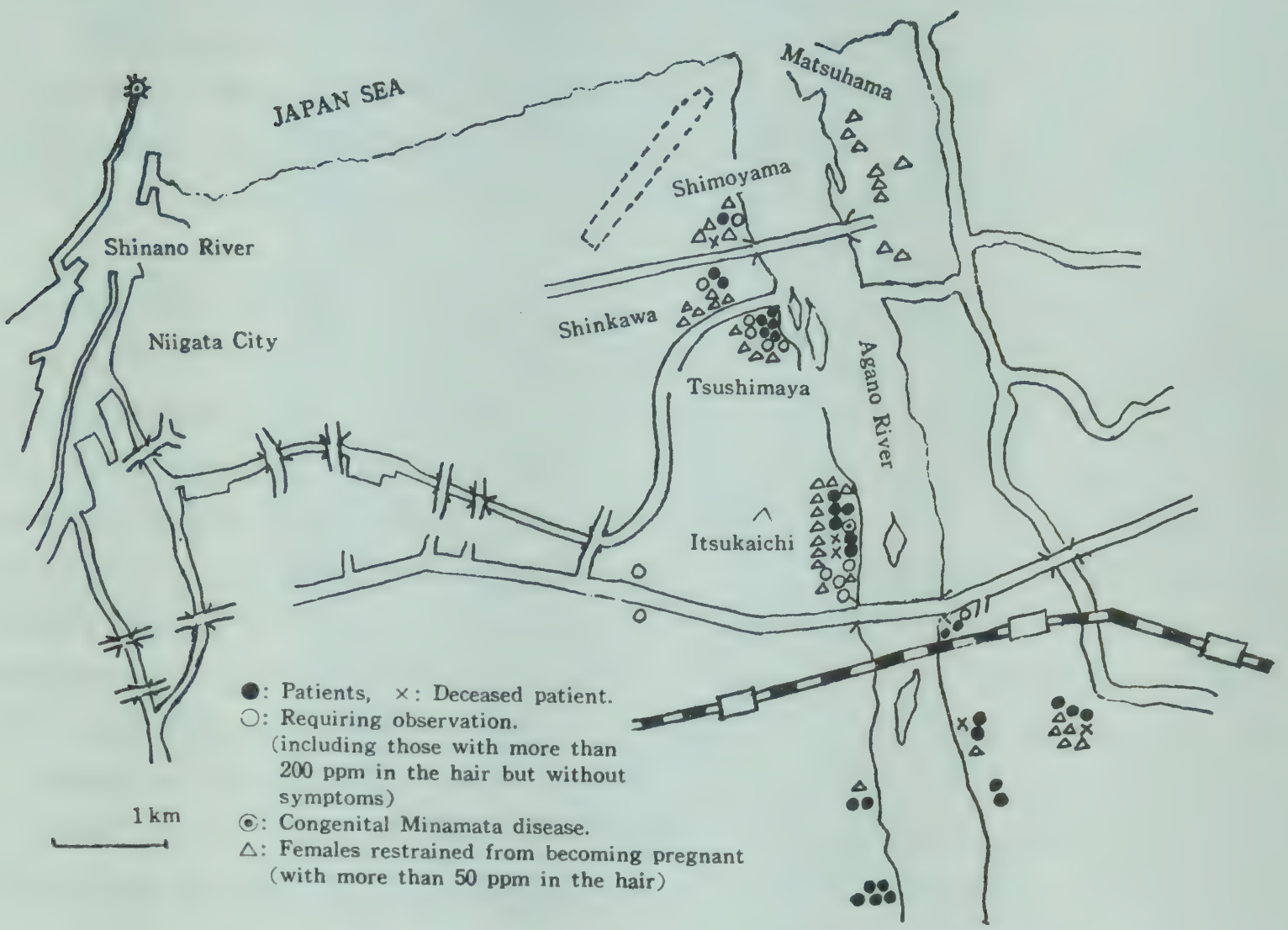
In 1964 and 1965 a mass outbreak of Minamata disease occurred in a fishing village on the lower Agano River, Niigata Prefecture. It was officially discovered in June 1965. During the same year, 30 patients were diagnosed positively (Tsubaki, T.; 1968). The patients are being found even now, and about 800 are registered (Shirakawa, K. et al; 1973). The cause was methyl mercury discharged from an acetaldehyde plant of the Showa Denko Company, 60 km up the Agano River. In this, the second Minamata disease incident, nursing babies were immediately put on artificial feeding, and females with more than 50 ppm of mercury concentration in the hair were assisted to avoid pregnancy (Fig. 17). Forty-seven females already pregnant were examined several times afterwards. Such early countermeasures had the desired effect, and only one case of congenital Minamata disease (outlined below) has been reported in Niigata.

Case history

T. F., female, born on March 27, 1965. Her uncle, who was living with her family, contracted Minamata disease around May 1965. Mercury concentration in the uncle's hair was 213 ppm. The mother's mercury concentration was 293 ppm. Pregnancy and delivery were quite normal. Weight at birth was 3 kg.

Subject was fed on mother's milk until she was two months old,

Fig. 17: Minamata Disease in Niigata.
(Distribution of Patients along Basin of Agano River)



then mixed feeding up to 6 months, and artificial feeding (milk) thereafter. Six months after birth she could clench her fists but could not grasp things. It was noticed that her neck was unstable. Eleven months after birth she was examined because she did not use her voice, could not sit up, and showed conspicuous hypersalivation. She was diagnosed as having cerebral palsy. Thereafter, her mental and physical growth lagged; only when she was one year old did she recognize her mother and show interest in toys. At 18 months her neck was still unstable, and she was bedridden. At 2 years 8 months she could stand when holding onto something, and at the age of 3 she could say a few words such as "ah", or "hai" (yes). At the age of 4 she was able to walk with someone supporting her, and to eat with a spoon. She can now call attention to toilet needs.

Clinical observation by the author as of February 1971: Pupillary reaction is normal. but there is internal strabismus. As she is told to gaze at a point, eyeballs move spontaneously (slow movements more than spontaneous nystagmus). No major disturbance in sight or hearing.

The neck is unsteady and the body moves back and forth even when she is seated. Athetosis and chorea are observed in the tongue, mouth, neck and fingers. Movement of the hands is slow, awkward and jerky, and fingers are deformed. Grasping reflex is seen in both hands, nose-finger test is disturbed, and adiadochokinesia and dysmetry

are seen. Muscle tone is rigid, lower limbs are crossed, and the knees and joints of the feet are contracted. She can walk with equipment. Feet show talipes equinus. Muscle-stretch reflex is exaggerated and Babinski's sign and Rossolimo's sign are positive. Speech is drawling and inarticulate. She can utter only a few words, but understands most words spoken by others. Mental age is 2 to 3 years, or that of an idiot.

At the time when the patient was discovered, there had been an outbreak of Minamata disease in the same area and even in the same family. The mother had eaten a large quantity of fish contaminated with methyl mercury during her pregnancy, and the mercury concentration in her hair was 293 ppm. During pregnancy and at delivery no other factor capable of causing a cerebral abnormality was noticed. Seventy-seven ppm of mercury was detected in the hair of the patient herself. Because she had been taking Penicillamin by prescription, the mercury value in her urine had increased to between 696 and 1,272 μg/1. Clinically, the infant showed the same symptoms as those of congenital Minamata disease patients in Minamata. On the basis of the findings mentioned above she was diagnosed as having congenital Minamata disease.

IV. A CASE OF CONGENITAL METHYL MERCURY POISONING IN NEW MEXICO

A similar outbreak of organic mercury poisoning occurred in a farm family in Alamogordo, New Mexico. The author visited the home in March 1975 and examined the patients directly.

In 1969, seed grain treated with methyl mercury fungicide (containing 32.8 ppm of mercury) was fed to pigs for one month. The pigs were slaughtered and the meat (contaminated with 27.5 ppm of mercury) was consumed by the family for about 3 months. As a result, three children, aged 8, 13 and 20 years, contracted serious methyl mercury poisoning. The decisive factor in the diagnosis was the high mercury value detected in blood, hair and urine of the patients, as well as in the seed grain and pork. One month after they had stopped eating the pork, mercury was detected at the rate of 1.92 ppm in the serum and 1,397.6 ppm in the hair of the 8-year-old patient. In the 13-year-old, 2.78 ppm was found in the serum and 2,436.0 ppm in the hair. Furthermore, administration of BAL (British Anti-Lewisite) had caused 0.50 to 0.49 ppm of mercury to be discharged in the urine of patients. (Pierce, P. E. et al. 1972)

When the 40-year-old mother began eating the contaminated pork, she was three months pregnant, and she continued to ingest methyl mercury until the embryo was 6 months in utero. By that time, the

Fig. 18: Congenital Methyl Mercury Poisoning in New Mexico.

Male aged 5 years was bedridden and mute.
(Photographed by Harada, M. in March 1975.)

mercury concentration in the mother's serum was 2.91 ppm. Two months after she stopped eating the pork (when the fetus was in its 8th month), the mercury count had dropped to 0.47 ppm in the serum and 0.18 ppm in the urine. No other abnormality was observed during pregnancy, but the baby was in syncope for one minute at birth. Weight at birth was 3,062 g. Mercury in the amniotic fluid was 21 ppb. In the infant's urine 2.7 ppm of mercury was detected one day after birth, 2.0 ppm four days later and less than 0.01 ppm 6 weeks later. Several days afterward, intermittent gross tremor of the newborn's extremities was observed. The crying voice was weak, the baby was fretful and the muscle tone was hyperactive. Six months after birth there was onset of grand mal. Thereafter, development of mental as well as motor functions stopped. At present the baby is bedridden and mute (Fig. 18).

Clinical observation by the author in March 1975: Male, 5 years old. Height 90 cm, circumference of the chest 45 cm, nutritional deficiency conspicuous. He was bedridden and could not sit up or speak at all. He showed nictitating reaction to photographic flashs or loud sounds. Distortion of posture was extreme and muscle tone highly rigid. Muscle-stretch reflex was hyperactive and pathologic reflexes were seen. In the hands, toes, head and many other parts of

the body, slow chorea and athetosis were observed. Primitive reflex was visible. Spontaneous nystagmus was observed but patient did not follow lights. He was in a state of complete akinetic mutisn. At present grand mal occurs once a month, and myoclonic jerk often. The mother complained of various subjective conditions such as headache, but symptoms were mild.

V. INTRAUTERINE POISONING BY PCB (POLYCHLORBIPHENYL)

A. PCB-contaminated rice-bran oil incident

In the summer of 1968 there was a mishap in which rice-bran oil heavily contaminated with PCB was sold in Kita Kyushu and other parts of Japan. This was caused by the Kanemi Oil Co. in Kita Kyushu. While rice-bran oil was being processed, a large amount of PCB (Kanechrol 400) coolant seeped into the oil. This is called the Kanemi Oil Incident. The number of those affected was not counted exactly but more than 3,000 persons were officially included. In the case of adults, patients ingested rice-bran oil contaminated with 2,000 to 3,000 ppm of PCB for an average period of 5 months. The average threshold of onset was 2,000 mg of PCB, and the minimum threshold was 500 mg. The average adult patient was calculated to have ingested 67 μg/kg a day per 50 kg of body weight (Isono, N.; 1972). Poisoning in adults was characterized by dermatological symptoms. The syndrome described as follows by Goto et al. (1969)

Clinical signs: There were many patients who complained of the swelling of upper eyelids, anorexia, languor, the feeling of numbness, edematous swelling of limbs, nausea, vomiting, lumbago, pain in joints, and heels pigmentation of lips, abnormal menstruation, and impotence. There were various kinds of skin disease, especially chloracne associated with follicular keratosis.

a) Ophthalmic findings: Uneveness in the line of the eyelids, swelling of Meibom gland, pigmentation of cornealring and conjunctiva, hypersecretion of cheeselike discharge from the eye.

b) Dermatological findings: Acneform eruption, marked enlargement and elevation of follicular openning, pigmentation and flattening of nails, pigmentation of skin, lips, gingiva and mucous membrane of oral cavity, formation of hyperkeratotic plaque in sole and palm, hyperhidrosis, hypertrichosis, swelling of Montgomery gland in the breast, cyst formation of sebaceous glands in the genital region; in children, dry skin, milia at the site of joints.

Changes in the skin seemed to be based on hyperkeratinization associated with abnormal lipid metabolism. Individual lesions of acneform eruption ranged from the size of a pinhead to that of a pea.

They were pale, straw-colored cysts in the form of cysts filled with keratinous material and very small amount of sebaceous material. In hair follicles, follicular openings were enlarged and a filled with keratinous material. There was considerable secondary infection of staphylococcus epidermidis, forming large abscesses and lesions such as infections atheroma. There were some cases of hemispheric tumor in joints.

Later it became apparent that PCB poisoning caused not only dermatological symptoms but also disorders of the whole body (Uzawa, H.; 1969, Kuroiwa, Y.; 1969, Okumura, M.; 1969). Symptoms already confirmed include disturbances of cholesterol metabolism, liver function, respiration, peripheral nervous system, and cardiac function. Some

Fig. 19: Small Stature and Dark Brown Pigmentation in PCB Induced Fetopaty (Right), Compared with Control New Born Baby (Left).

Fig. 20: Dark Brown Pigmentation and Desquamation on the Skin and Hepatomegaly in Fetopaty Case.

infants were poisoned by PCB through the mother's milk.

B. Polychlorbiphenyl-induced fetopathy (Yamashita, F.)

Fetuses of mothers who ate vegetable oil contaminated with PCB were poisoned. Mass outbreaks occurred in Kita Kyushu and Nagasaki. Because the children were born with dark brown skin resembling the color of cola drinks they were called "Coca-Cola babies." Although the mothers ingested 0.3 to 0.6 liter (2,000 to 3,000 ppm) of the oil, their symptoms were mild. The weight of newborns was remarkably low (2,150 to 3,100 g) (Fig. 24). Clinical symptoms were described as follows by Yamashita et al (Funatsu, I.; 1972, Taki, T.; 1969, Yamaguchi, A.; 1971).

1) Dark brown pigmentation (skin in general, lips, gingiva, genitalia, axilla); 2) Gingival hyperplasia; 3) Dentition at birth; 4)

Fig. 21: Edematous Eyelid

Fig. 22: Gingival Hyperplasia with a Teeth at the Birth.

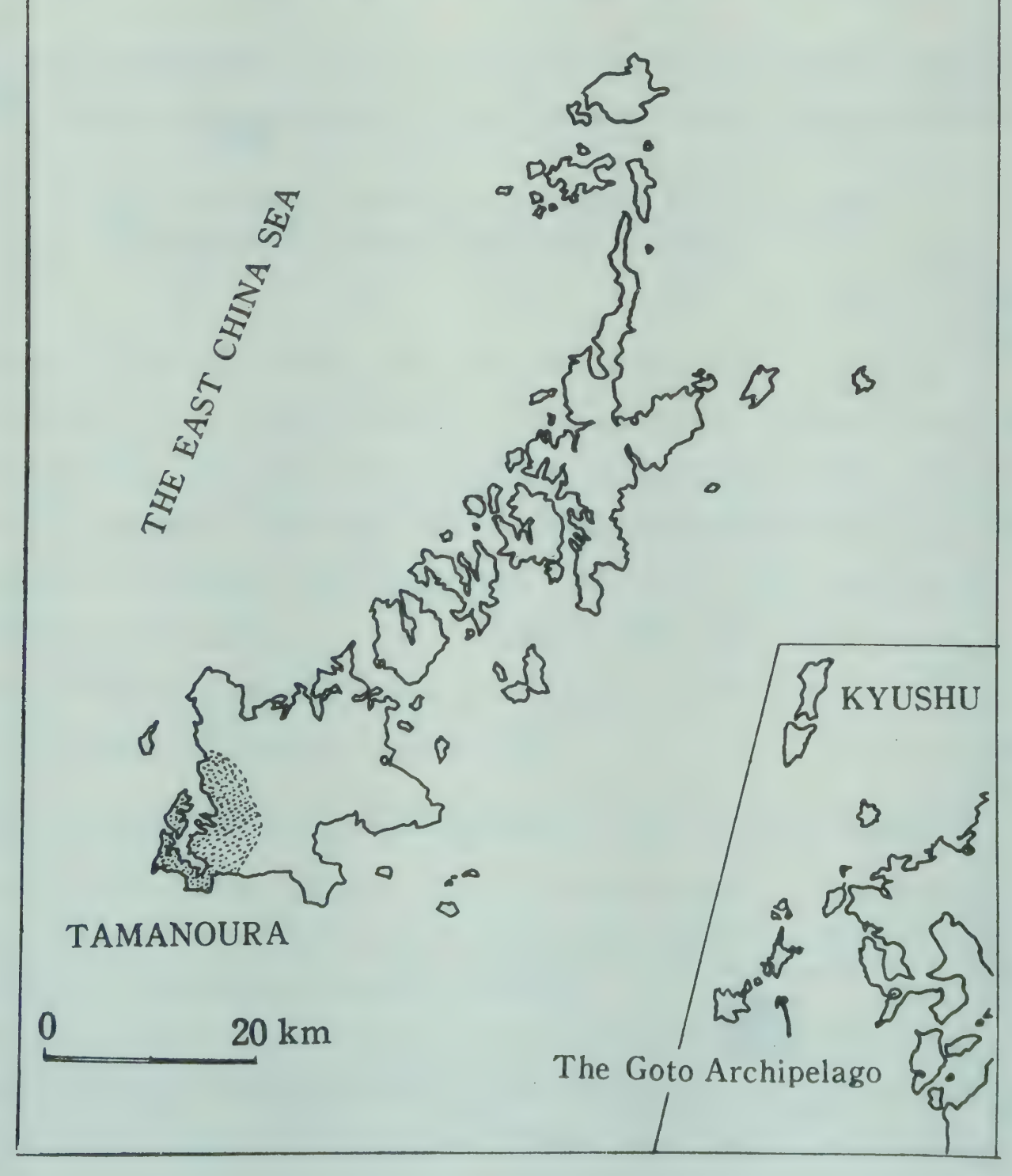
Calcification of skull; 5) Wide, open sagittal suture of skull; 6) Color ring on limbic cornea; 7) Desquamation (perchment-like); 8) Edematous eyelid; 9) Secreta on conjunctival palpebra (Fig 19, 20, 21, 22).

These patients had been regarded as being without neurological and mental deficiencies. or mild one at worst.

C. Neurological and mental follow-up survey

In 1974 the author conducted follow-up surveys on neurological and mental aspects of the illness in the Tamanoura area of Nagasaki Prefecture, where many " -Cola babies" were found. Tamanoura Town (Pop. 3,978) is on an island, and is relatively isolated. For

Fig. 23: Map of Tamanoura, Nagasaki Prefecture.



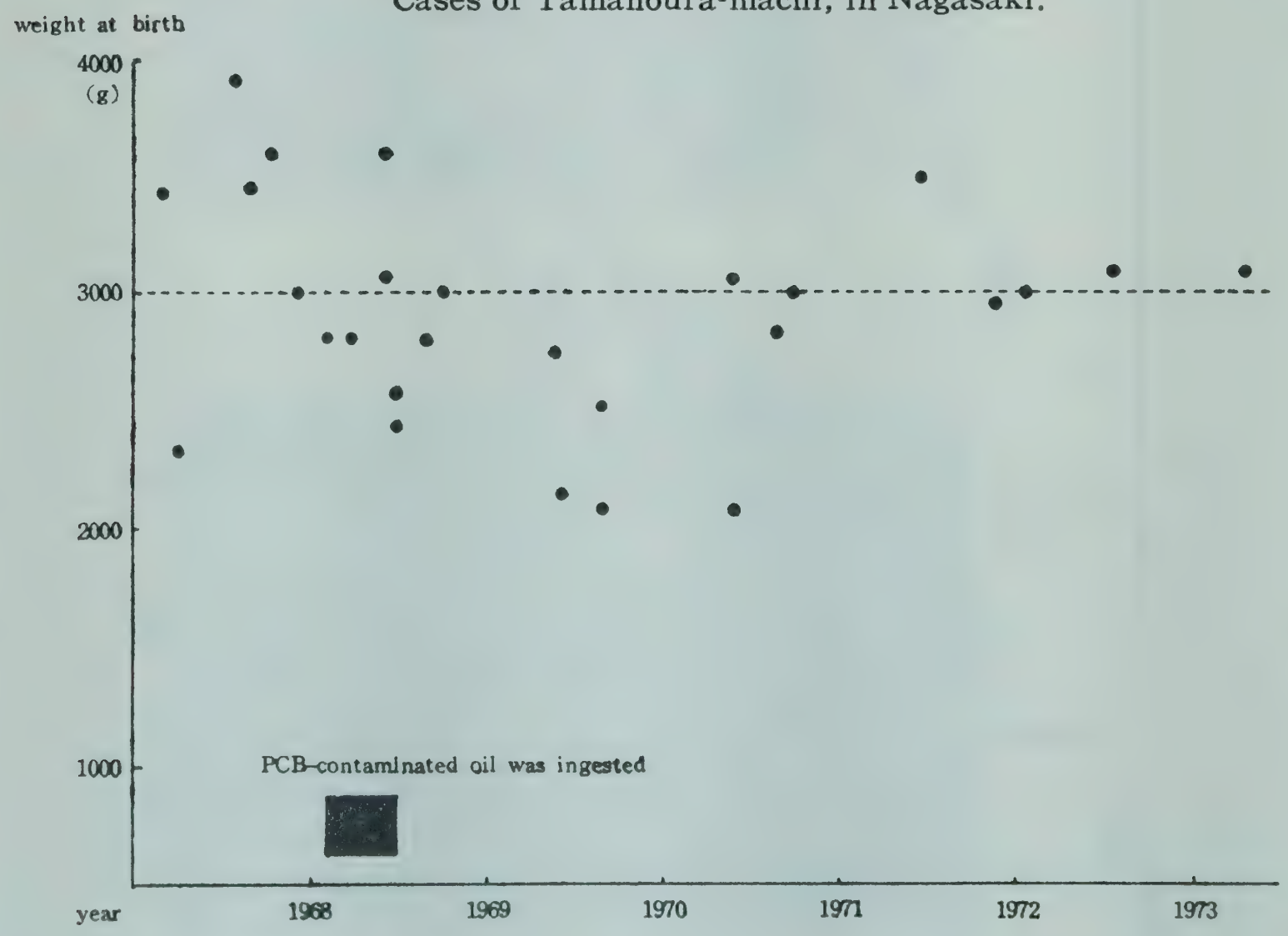
about six months from March 1968, when PCB-contaminated oil was introduced, nearly all of the inhabitants used it in their diet (Fig. 23). The author investigated 127 children, divided into three groups: those who ingested contaminated oil directly, those polluted by PCB through mothers milk, and those affected in utero. Among those in the last-named group, some were poisoned by PCB-contaminated oil ingested by the mother during pregnancy, and others were affected by residual PCB in the mother's body. There were 34 patients who seemed to have been poisoned in utero. Of these, two died, one was stillborn, and the remainder were still living in Tamanoura. The author was able to examine 27, whose ages ranged from 4 to 7 years (Table 7).

Table. 7 Subjects of PCB Poisoning
(Tamanoura-machi, Nagasaki Prefecture in 1974)

Aquired infantile PCB poisoning	PCB poisoning through mother's milk	Congenital PCB poisoning (PCB induced Fetopathy)	
		Directly in fetal period	Due to residual PCB
100 cases	9 cases	5 cases	13 cases

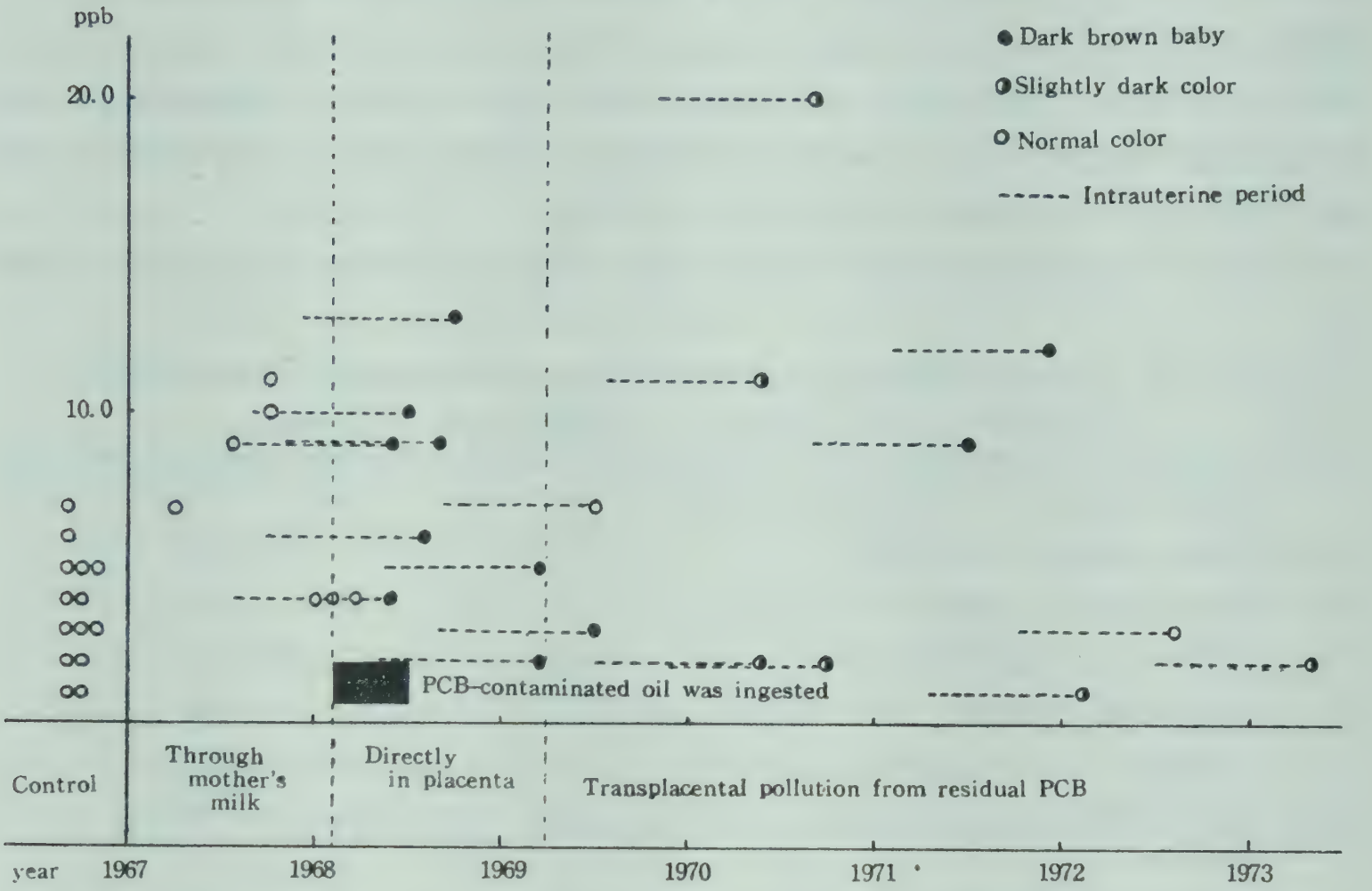
If one judges solely from body weight at birth, it appears that residual PCB in the mother's body remains toxic effects for two years (Fig. 24).

Fig. 24: PCB Pollution and Weight at Birth.
Cases of Tamanoura-machi, in Nagasaki.



That is, after ingestion of PCB-contaminated oil by the mothers, the body weight of newborn babies was apparently smaller. Even after ingestion had been suspended, reduced body weight at birth was observed untill the end of 1970. As of August, the PCB value in the serum of these children was relatively high, and it is suggested that " -Cola babies" could continue to appear for a long time (Fig. 25).

Fig. 25: Infantile PCB Poisoning through Mother's Milk, Congenital PCB Poisoning and Residual PCB in Blood Plasma. (Harada, M. & Takamatsu, M.)



According to Fig 25, even after the mother stopped eating PCB-contaminated oil, " -Cola babies" were observed among those born at the end of 1971. Slightly brown babies were seen in 1973. In addition, as late as August 1974 the PCB value in blood was high in both mothers and children, indicating that once PCB has entered the body it is difficult to discharge. As of August 1974, the PCB value in blood of these children's mothers was 3 to 33 ppb. (PCB were measured by Prof. Takamatsu, Kurume University)

D. Clinical symptoms of PCB patients after a long interval

Seven years have passed since the outbreak. Clinical symptoms of these children, seemingly, were relatively mild compared with those of congenital Minamata disease patients.

Dermatological symptoms have improved, but pigmentation of skin, lips and gingiva, pigmentation and flattening of nails and hypersecretion of the eyes still remain (Table 8). Such noteworthy symp-

toms as malformation of teeth, cyst formation (Lipoma etc) and multiple fracture also persisted. Among recognized symptoms still continous are chronic bronchitis with coughing and sneezing, abdominal pain, headache, fever from unknown causes, and cardiac disturbance such as arthralgia (Table 9).

Concerning neurological symptoms, disturbance of the autonomic nervous system, nutritional deficiency and growth impairment are observed. Abdominal pain, diarrhoea and headache are especially noticeable. The pattern of these symptoms resembles what is called autonomic epilepsy. Inarticulate pronounciation is moderate. It is difficult to find clinical signs at the neurological level, but slowness, jerkiness and clumsiness of action are observable. Compared with congenital Minamata disease, intellectual disturbances are milder, and the average IQ of patients is around 70.

From the viewpoint of clinical psychiatry salient defects are ener-

Table. 8 Dermatological Symptoms in Chronic Stage of PCB Poisoning of Children (127 cases). —— Seven-year Follow-up.

Pigmentation of the gingiva, lips	75
Pigmentation of the nails	49
Flattering of nails	46
Hypersecretion of the eye	45
Acneform eczema	38
Scarring	23
Blackheaks	5
Tumor	7
Fracture of bone*	5

* not dermatological

Table. 9 Subjective Symptoms of PCB Patients in Chronic Stage

	Congenital cases	Nursing infant	Infantile cases
General fatigue	4	4	59
Cough, phlegm	11	4	48
Abdominal pain	7	4	43
Headache	6	3	39
Numbness	1	2	32
Abnormality of teeth*	8	5	28
Vertigo	0	0	25
Fever*	6	1	14
Pain in limbs and joints	2	1	11
Total	18	9	100

* not subjective symptoms

vation, lack of edurance, hypotonia, apathy, and behavioral disorders caused by insensitivity. These children seem sullen and expressionless, lacking the brightness or liveliness characteristic of normal children. Furthermore, they lack perseverance, and a characteristic difficulty in concentration is observed in their daily life. It is quite possible that these behavioral characteristics are due to affective blunting caused by secondary mental retardation (Table 10).

E. Case histories

Case 1.: Mother, 41 years old, ingested about 1.2 liter of PCB-contaminated rice-bran oil in February and April 1968. Mother and four elder siblings contracted PCB poisoning in begining of April 1968. A girl born to her on June 31, 1968, was breast fed. The baby showed intrauterine retardation of growth (weight at birth was 2550 g). Dark brown pigmentation of the skin and mucous membrane, especially skin of the genitalia, axilla, finger nails, hair follicles and mouth were observed. Edematous face and limbic conjunctiva and gingival hyperplasia were seen too. The patient was a so-called "Coca-Cola baby". Disturbance of growth and nutrition were noticed. At 14 months she was able to walk without help. At about this time, tonic convulsion with fever was seen. The dermatological symptoms began to improve between the ages of 3 to 5 years. Observed in 1974, at 6 years, were moderate pigmentation of gingiva, finger and nails, deformities of fingers, hyper-secretion of eyes, nutritional deficiency, chronic bronchitis, growth impairment, headache and paroxysmal abdominal pain.

Table. 10 Neurological and Mental Symptoms in Chronic Stage of PCB Poisoning

	Congenital cases	Patients through mother's milk	Infantile cases
Autonomic nerve symptoms	8	1	33
Paroxysmal symptoms	5	1	23
Nutritional & growth disorder	8	6	9
Disturbance of peripheral nerves	0	0	4
Jumbled speech	5	1	0
Auditory disturbance	1	2	2
Enervation, fatigue	5	5	47
Hypotonia	6	4	41
Lack of positiveness	4	4	37
Depression	0	0	8
Poor concentration	6	3	16
Mental retardation	8	2	14
Total	19	9	100

Also, hyperhydrosis and clumsiness of action are seen. Slight mental retardation (IQ; 80), hypokinesis, apathy, difficulty in concentration and lack of perseverance are recognized. The concentration of PCB in her plasma was 6.0 ppb in 1974.

Case 2.: Mother, 39 years old, ingested about 1.2 liter of rice-bran oil PCB-contaminated in March and April 1968. Her husband and two of her children also were poisoned by PCB. The concentration of PCB in the mother's plasma was 18.0 ppb in 1974.

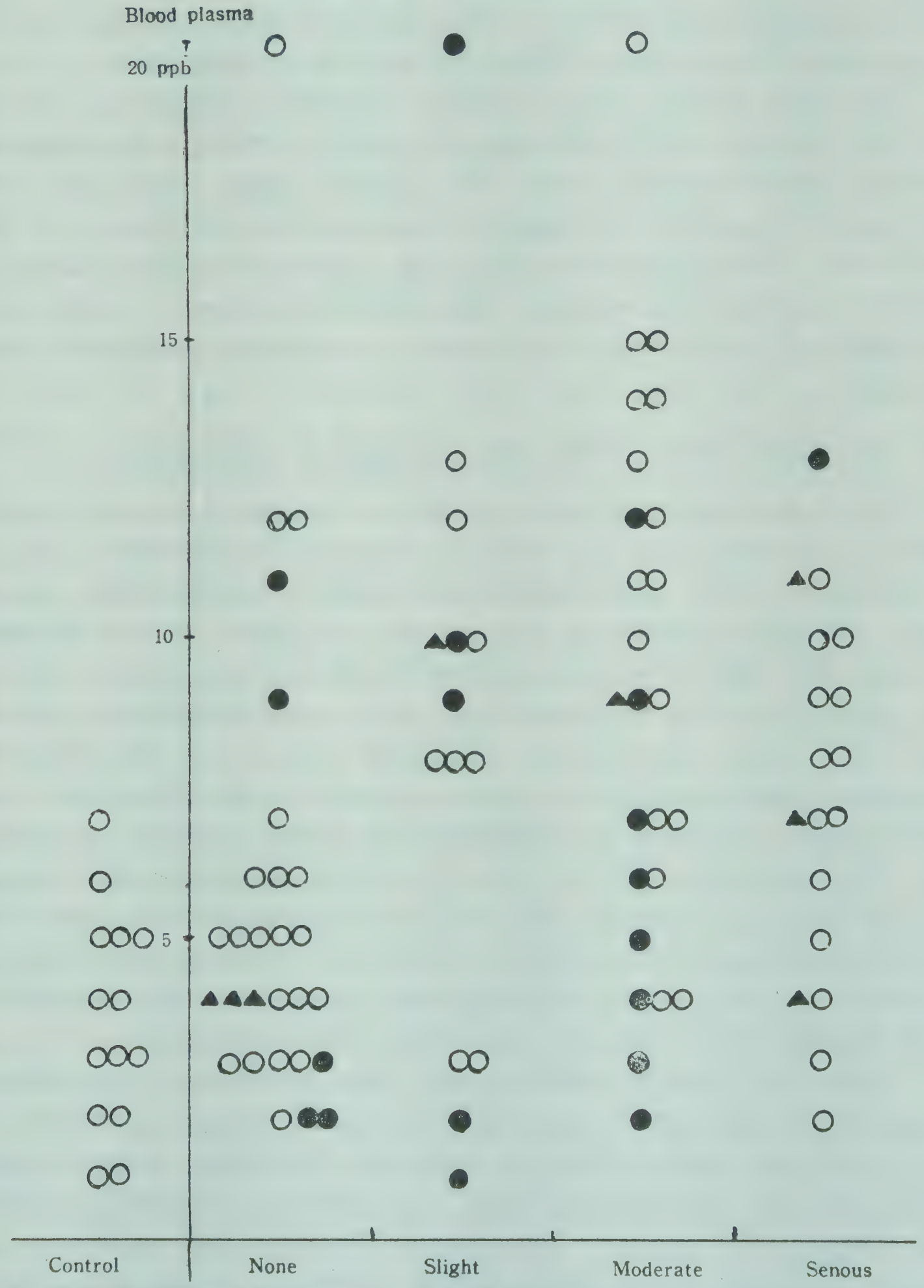
A girl born to her on January 19, 1968, was breast fed. Weight at birth was 2,700 g. At 6 years, moderate pigmentation of gingiva, fingers and nails and hypersecretion of the eyes is observed. There is no problem neurologically, but three bone fractures have resulted from relatively slight accidents. She appears enervated, apathetic, expressionless and absent-minded. She does not smile, looks tired, and does not speak. Complains of weariness and headache. She does not go out to play, preferring to lie down at home. The concentration of PCB in her plasma was 4 ppb in 1974. The patient contracted PCB poisoning through the breast feeding.

Case 3.: On May 5, 1969, a boy was born to the same mother. Weight at birth was 2,750 g, artificial feeding. Dark brown pigmentation of the whole body and keratodermia were observed at birth. The dermatological symptoms began to improve around the second month, but growth has been delayed somewhat, and it was not until 18 months after birth that he stood up; he was late to speak, and even now his pronounciation is inarticulate. There is light pigmentation of the whole body, gingiva and fingers as well as flattened nails and exanthema, an eruption. On the right side, **L. C. C.** was visible. The patient had asthma and caught cold easily. He often suffers from abdominal pain, and hypersecretion of the eye is conspicuous. There is no severe neurological disturbance, but motions are slow and clumsy. He is absent-minded, and the mouth remains half-open. He is restless and concentrates with difficulty. He is dull and appears depressed. PCB in the plasma was 5 ppb in 1975, and IQ was about 60. The patient contracted poisoning caused by residual PCB in mother's uterus.

Psychiatrical observations: Mental deficiency of congenital PCB-poisoning patients is milder than that of congenital Minamata disease patients. But we cannot be sure that abnormal metabolism will not affect their health in future. At present, the psychiatric problems of those affected children are behavioral abnormalities due to disturbances of emotion or will. Secondary effects due to internal disorders of the whole body should be considered. But since residual PCB still registers high values, its direct effect cannot be denied. The author and Takamatsu made comparisons of clinical observations and PCB values in

the blood (Fig. 26). Although there are some exceptions, there was a positive correlation between the degree of PCB values in the blood and the severity of behavioral disorders. But among older children, i. e. patients who suffered acquired PCB poisoning, some showed low PCB values in blood despite severe symptoms. In terms of individual observations, neurotic reactions are seen in some cases, and it has become clear that these were caused by dermatological or internal

Fig. 26: Residual PCB in Blood Plasma and Behavioral Disorder.
(Harada, M. & Takamatsu, M.; 1974)



F: ● PCB-induced Fetopathy, ▲ PCB Poisoning through mother's milk,
○ Acquired infantile PCB Poisoning.

symptoms. In relatively young congenital PCB-poisoning patients or those poisoned through mother's milk, this tendency is not seen.

It has become apparent that since PCB in the blood is measured by gas chromatography, there are many different PCB patterns (Takamatsu). In Japan the environment is contaminated by PCB, and among controls some show relatively high PCB values in the blood. But the PCB in question here is Kanechrol 400, which was involved in the Kanemi oil incident, and it showed its characteristic pattern in gas chromatography. Therefore, according to the patterns in gas chromatography, even small amounts can be proven if the subject ingested PCB-contaminated Kanemi oil. The test was quite efficient for diagnosis since PCB remained within the body for a long time.

The blood plasma of the mothers of these children was contami nated at the rate of 3 to 33 ppb. Generally speaking, the symptoms of these mothers tended to be mild. But the more severe the symptoms of the mother, the more conspicuous the symptoms of their newborns. Even after symptoms of the mothers improved, "Coca-Cola babies" continued to be born, and this is significant. Furthermore, followups of these children in regard to metabolic deficiency will be necessary.

VI. SIGNIFICANCE OF TRANSPLACENTAL POISONING

It was shocking to us to learn that toxin absorbed into the mother's body is transmitted to the embryo through the placenta. Like the blood-brain barrier, the blood-placenta barrier was generally regarded as an effective obstacle to the transfer of toxin. Before Minamata disease was discovered, the possibility of mercury passing through the placenta had been pointed out, but researchers were not very interested in it. Concerning Minamata disease, in 1961 Morikawa succeeded experimentally in creating symptoms of Minamata disease in the brains of kittens by administering methyl mercury to pregnant cats (Morikawa, N.; 1961). Also, Dr. Morikawa gave methyl mercury to rats (0.2 to 1.0 mg per 100 g of body weight) and to cate (0.5 to 1.0 mg per kg of body weight) during early and late pregnancy. He demonstrated that when relatively large doses were administered over long periods, stillbirths and miscarriage were numerous.

From these facts it appears that when a mother is contaminated with methyl mercury in the early stages of pregnancy, but not sufficiently to cause miscarriage or stillbirth, offspring may be affected with congenital Minamata disease. By accumulating mercury through the placenta, the embryo lightens the effect on the mother to some extent. In other words, toxin which is difficult to discharge from the mother's body is transmitted to the embryo through the placenta.

The following examples indicate the correlation.

Case histories

Case 1.; K. T., born on December 16, 1929. Wife of a fisherman, family residing in Modo. Father-in-law living with her was also a fisherman; he contracted Minamata disease in February 1957 and died on January 23, 1971 after a serious illness. Mother-in-law is suffering from Minamata disease and is being treated. Patient's husband (born in 1933) is suffering from Minamata disease with sensory disturbances of perioral area and extremities, tremor, auditory deficiency, constriction of visual fields, and incoordination. The patient became pregnant nine times. The first child (female), was born in 1948 and is healthy. But a grandchild born in 1964 to the first daughter is suffering from cerebral palsy and is suspected of having congenital Minamata disease. The second child (male) was born in 1954 but died in February 1956 with encephalopathy marked by convulsion and blindness. There was strong suspicion of Minamata disease in this case also.

In May of that year, Minamata disease was officially verified. The third and fourth children, twins, were born in August 1956, but the third one was a stillbirth. The fourth child did not move its limbs at all and died on the 12th day. Again, congenital Minamata disease was suspected. In 1956 the outbreak of congenital Minamata disease involved many patients, and in this district (Modo, Udo and Tsukinoura) 9 were discovered. In 1957 she miscarried in the third month, and in January 1958 the fifth child was born. Neurological symptoms were not apparent, but a slight mental retardation was seen. Subsequent pregnancies ended in miscarriage in 1959 and 1960. In January 1961 the sixth child was born but died three days later. In 1962 she miscarried again. Thus, out of nine pregnancies there were three newborn's deaths (including twin) in which congenital Minamata disease was suspected, four miscarriages and one child seems to have infantile Minamata disease. Despite the fact that three family members living under the same roof are suffering from Minamata disease, ranging from moderate to typical and severe cases, K. T. is not affected seriously although she shared the same fish eaten by the others. Her symptoms are sensory disturbances in the limbs, slight deafness, muscle weakness and hypotonia of muscles.

At present, those who are regarded as congenital Minamata disease patients are in serious condition. In all cases, the mothers were contaminated by methyl mercury directly during their pregnancy. But as it was pointed out in references to PCB poisoning, toxins difficult to discharge from the body still remain even after the mother stops ingesting the poison; and it has been demonstrated that, during

Fig. 27: Case of H. K.

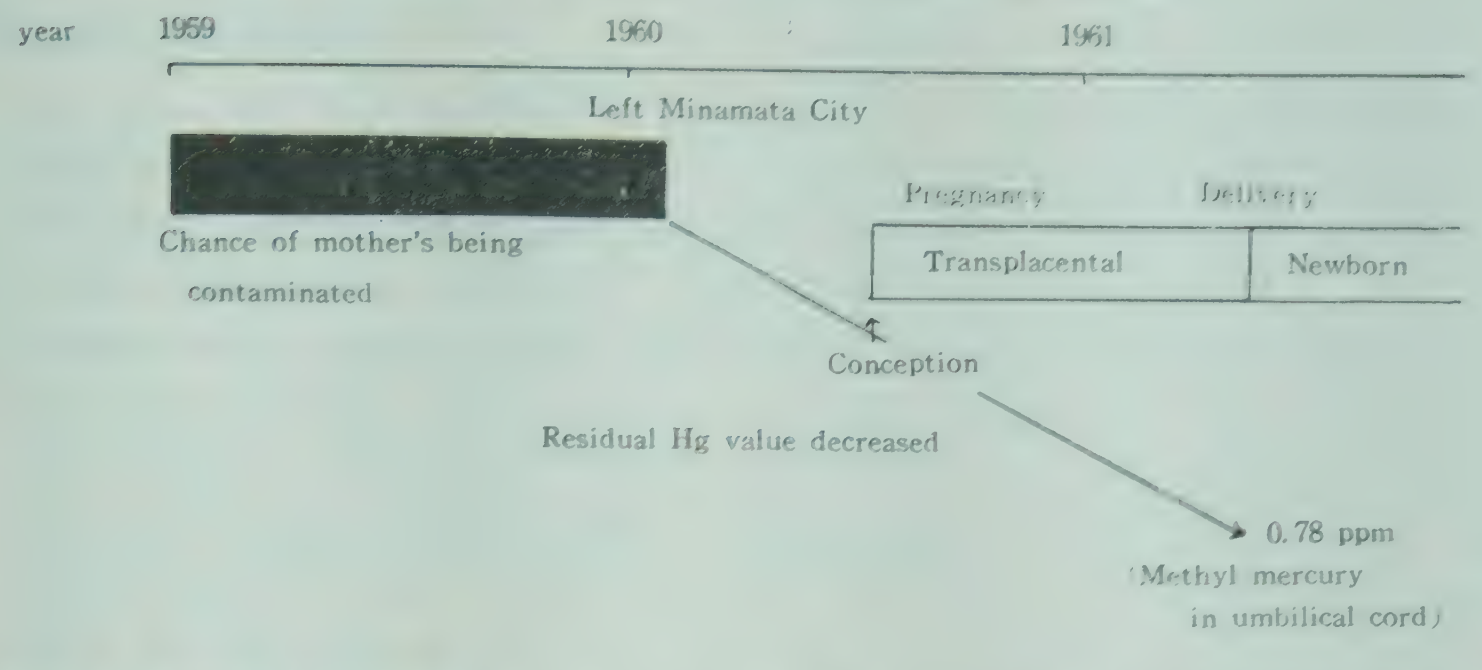
Male aged 14 years. Mental retardation, microcephalus, incoordination, nystagmus, hyperkinesia, deformities of fingers and vertebra, dysarthria and hypersalivation etc were observed.

pregnancy, residual toxins can affect the embryo.

Case 2.: H. K., male, born on April 7, 1961. Until January 1960 the mother lived in Minamata and ingested large quantities of fish supplied by her elder brother. In January 1960 she married and moved to F. City. Soon she became pregnant. No abnormality was observed during pregnancy, and she was delivered in the 10th month. For several minutes the baby was in syncope. Weight at birth 3.6 kg, breast fed. One year later it was noticed that the baby was mute, and his neck was unsteady. At two years the neck had become steadier and the child could sit up. At about this time, myoclonic jerk was seen. At five he was able to speak some words, and through rehabilitation he became able to walk with equipment. Since 1967, grand mal has been observed once in 4 years. As of January 1975, the neck was unstable, leaning toward right. Chorea and athetosis are conspicuous in the mouth, neck and limbs, and become especially noticeable upon voluntary movement. Nystagmus, slight strabismus, deformities of fingers and vertebra, hypersalivation, inarticulate pronounciation, primitive reflexes and muscular rigidity (toward the right), are observed (Fig. 27). IQ is 70. The pattern of onset in this case resembles that shown in Fig. 19.

It cannot be concluded immediately that this case is congenital Minamata disease caused by residual mercury in the mother's body.

Fig. 28: Curve of Residual Mercury in the Body and Effect on Embryo. (The Case of H. K.)



But it is very important to remember that methyl mercury at 0.78 ppm was detected in the umbilical cord of this patient.

Dr. Deshimaru proved in 1969, using rats, that polluted mother's milk could damage the brain of the child. Therefore, it could not be denied that congenital Minamata disease patients might have been poisoned by methyl mercury through mother's milk. However, indisputable cases of toxicity through mother's milk have not yet been found.

Pathological observations by Prof. Takeuchi indicate the possibility of damage in the early prenatal period, and the major cause seems to be contamination through the placenta.

There is a question as to whether or not this poison would affect chromosomes. It has been proven experimentally that methyl mercury sometimes causes abnormality in chromosomes of lower animals or plants. However, chromosomal abnormality of patients in Minamata has not yet been proven (Harada, Y.). Three cases of Down's syndrome were discovered in Minamata, but they are not thought to be connected with methyl mercury. (These cases are excluded from classification as congenital Minamata disease.) However, this possibility must be studied in future. If methyl mercury should be found to cause chromosomal abnormality, the new disease should be clearly distinguished from the congenital Minamata disease discussed here. As already mentioned in connection with mercury values is the umbilical cord, if there is intrauterine contamination, even in amounts insufficient to cause the disease, serious symptoms may be exhibited if child is similarly contaminated subsequently. If the second toxin differs from the original one, the problem will be complicated further.

VII. SIGNIFICANCE OF THE PROBLEM

The fact has been established that poison invading the mother's

body and passing through the placenta may seriously damage the brain and nervous system of an embryo. Yet in many such cases, the mother's health is not seriously affected. This situation is especially characteristic of congenital Minamata disease.

The condition and circumstances of patients with mental deficiency, emotional disturbance and neurological abnormalities have been described. In these serious cases, the possibility of methyl mercury poisoning is apparent. The clinical and epidemiological manifestations of patients showing organic deficiencies of the brain or minimal cerebral dysfunction of embryonic origin have attracted worldwide attention, and therefore the significance of transplacental poisoning, as in Minamata disease, should not be overlooked. At a time when in many parts of the world the environment is being polluted by various toxins, the direct or residual effect of such toxins on the bodies and nervous systems or mothers and children is a matter requiring the most urgent attention. There is a strong possibility that pollution of the environment will become more serious, and if people were obliged to preserve umbilical cords at birth, the practice would be very helpful in medical research on prevention of intrauterine poisoning, I believe. Since this is not only a narrow medical problem but a broad social one as well, it is hoped that the unfortunate experience of the Japanese may promote research that will help to avert similar tragedies elsewhere.

(I am deeply grateful to the following colleagues who measured my materials.

Methyl mercury in umbilical cords were measured by Dr. Motoshi Fujiki, Hygienics, Tsukuba University and Dr. Susumu Nishigaki, Tokyo Metropolitan Research Laboratory of Public Health. PCB in the blood were measured by Prof. Makoto Takamatsu, Environmental Hygienics, Kurume University.

Photographs of PCB poisoning were provided by Prof. Fumio Yamashita, Pediatrics Department, Kurume University.)

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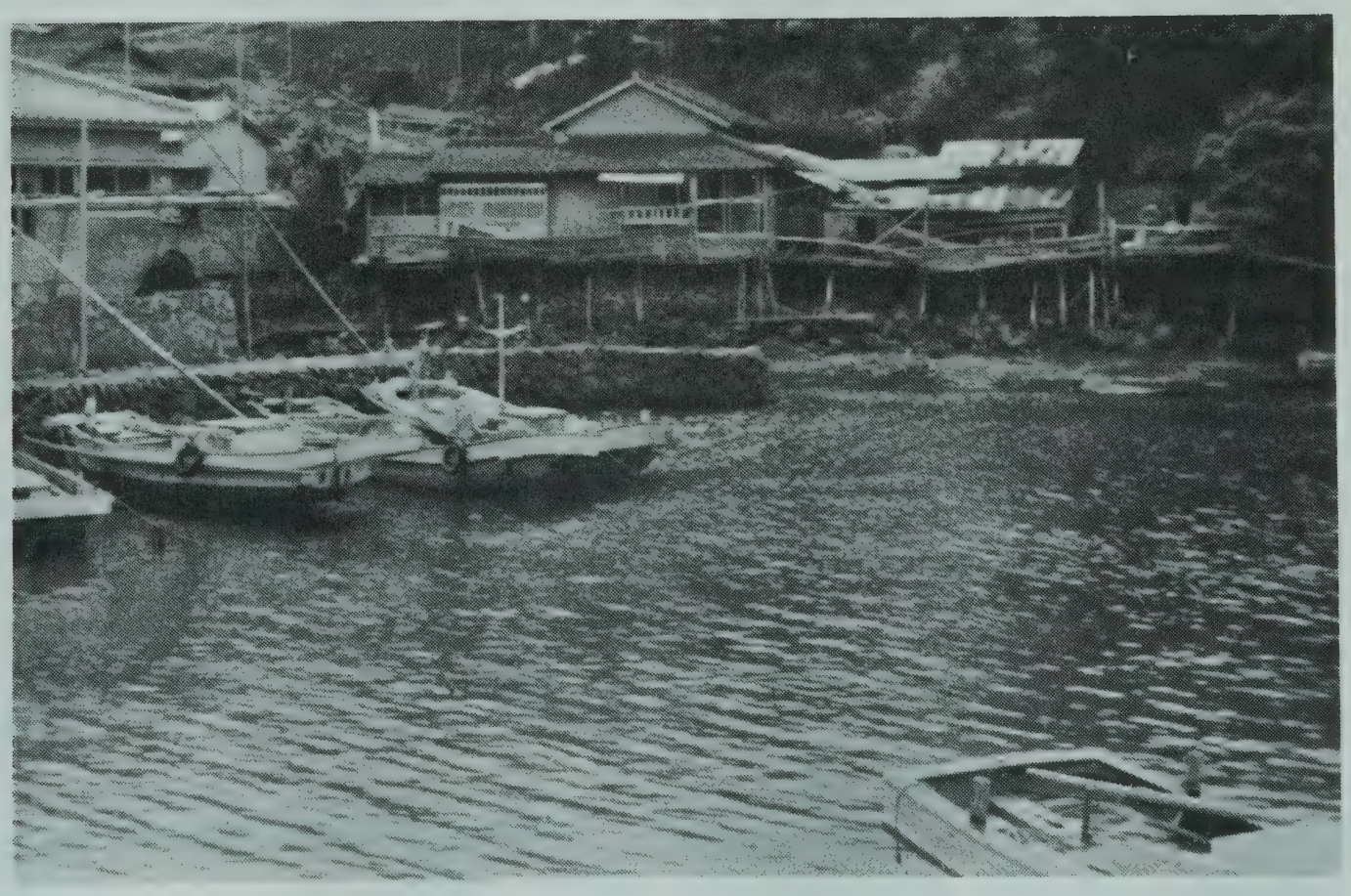

A Study on Methylmercury Concentration in the Umbilical Cords of the Inhabitants in the Minamata Area

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In 1970, the authors discovered that the umbilical cords of newborns were dried and preserved according to an old custom of Minamata and other regions. The authors collected 97 of those umbilical cords and measured the methylmercury concentration. Methylmercury was high in umbilical cords of inhabitantsborn in this area ; 0.51 to 0.99 ppm in 16 cases, 1.0 to ppm in 9, and more than 2.0 ppm (maximum 5.28 ppm) in 12.

These values were significantly higher than those of the controls (0.11 ± 0.03 ppm). During the period between 1954 and 1964, methylmercury showed the peak concentrations in the umbilical cords. Epidemiologically, it was correlated with the degree of environmental pollution and the amount of acetaldehyde production. Furthermore, methymercury concentrations were high in the umbilical cords of the patients with congenital Minamata disease. More than 0.5 ppm of methylmercury was found in 10 out of 12 cases. Methylmercury was high also in the mentally retaded patients born in the Minamata districts, whose neurological symptoms are not conspicuous. More than 0.5 ppm was found in 11 out of 16 cases. Consepuently, these cases are considered to be suffering from incomplete or atypical congenital Minamata disease.

In several cases of postnatal (acquired) Minamata diseases, the methylmercury concentration in the umbilical cords was high. It is suggested that in continuous poisoning caused by environmental pollution, such as Minamata disease, there are some patients who were contaminated by methylmercury in utero, later developed acute clinical symptoms by ingesting fish and shell-fish highly contaminated with methylmercury. High values of methylmercury were found in the umbilical cords from some apparently healthy individuals.

It is of utmost importance to demonstrate high levels of methylmercury concentration in the tissues from the patients who are suspected to have methymethymercury poisoning. Methylmercury in the umbilical cord may have some significance. However, it may be only an index of a transient contamination at a certain (perinatal) period, but not during the whole prenatal period (Author's abstract).

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Congenital Minamata Disease: Intrauterine Methylmercury Poisoning

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In 1955, many cases of severe neurological disease were found in the Minamata area of Kyushu, Japan. In 1959 it was demonstrated that the symptoms were due to poisoning by methylmercury, an effluent from an acetaldehyde plant of the Chisso Corporation. The toxin was transmitted through ingestion of seafood taken in Minamata Bay, hence the term "Minamata disease" (Study Group of Minamata Disease, Kumamoto University, 1968).

Meanwhile, in 1958, Professor Kitamura had discovered that in the district there were many infants, born after 1955, who showed symptoms resembling those of cerebral palsy. He stated: "It is possible that the substance causing the poisoning was transferred to the infants through the placenta or mother's milk, producing symptoms similar to those of Minamata disease" (Kitamura et al., '59; Kitamura et al., '60).

Thereafter, careful epidemiological and clinical studies were conducted (Harada, '64; Harada, '68), and pathological research as well (Takeuchi et al., '64; Matsumoto et al., '65), so that by 1962 the disease was identified as methylmercury poisoning via placenta. Subsequently, experimental findings confirming the fact have been made public successively (Morikawa, '61; Moriyama, '67; Fujita, '69). A long time was needed for reaching that conclusion because it was contrary to prevailing beliefs. It was thought that, as in the case of the blood-brain barrier, poison could not easily pass through the placenta, and that the fetus was thus protected. However, some poisons actually not only pass through the placenta but can also afflict the fetus without causing serious damage to the mother.

Congenital Minamata disease was first elucidated clinically in Minamata, but there have been some similar reports. Cases of cerebral palsy with mental deficiency are described in a report concerning poisoning caused by eating seed grain treated with alkyl mercury, announced in Sweden by Engleson and Herner in 1952. They suspected in this case that alkyl mercury had passed through the placenta. Perhaps this was the first description of what is now known as congenital Minamata disease. Reported thereafter were many cases in Minamata; one in Niigata, Japan (Harada, '76); one in New Mexico (Snyder, '71); and six cases in Iraq (Amin-Zaki et al., '74). Judging from these facts, congenital Minamata disease is not the problem of Minamata alone.

Manifestations

During pregnancy or at birth, no abnormality has been observed in mothers of affected children. No conspicuous abnormality has been seen in newborns' weight at birth or number of months in utero. Breast-fed infants were most numerous, and some had mixed feeding. It was at the beginning of the sixth month after birth that abnormalities were recognized. Symptoms were instability of the neck, convulsion, and failure of the eyes to follow. Patients developed severe neurological symptoms as well as mental symptoms. Observed at a high rate were common symptoms such as intelligence disturbance (100%), primitive reflex (100%), cerebellar symptoms (100%), disturbance of body growth and nutrition (100%), dysarthria (100%), deformity of limbs (100%), hyperkinesia (chorea, athetosis) (95%), hypersalivation (95%), paroxysmal symptom (82%), strabismus (77%), and pyramidal symptom (75%). Clinically, they showed similar clinical pictures with each other (figs. 1-4).

Such diffuse cerebral damage can be recognized not only in congenital Minamata disease but also in cerebral palsy caused by other factors. However, some symptoms are characteristic of the former.

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Fig. 1 Congenital Minamata disease patients in Minamata area. The patients showed very similar clinical picture to each other. (Photographed by M. Harada in 1962.)

Fig. 2 Neck is unsteady, inability to sit up. Male aged six years, born in 1956, died in 1969 without any improvement of symptoms.

Fig. 3 Deformities of limbs, nutritional deficiency, a condition resembling akinetic mutism. Female aged six years, born in 1956, died in 1962.

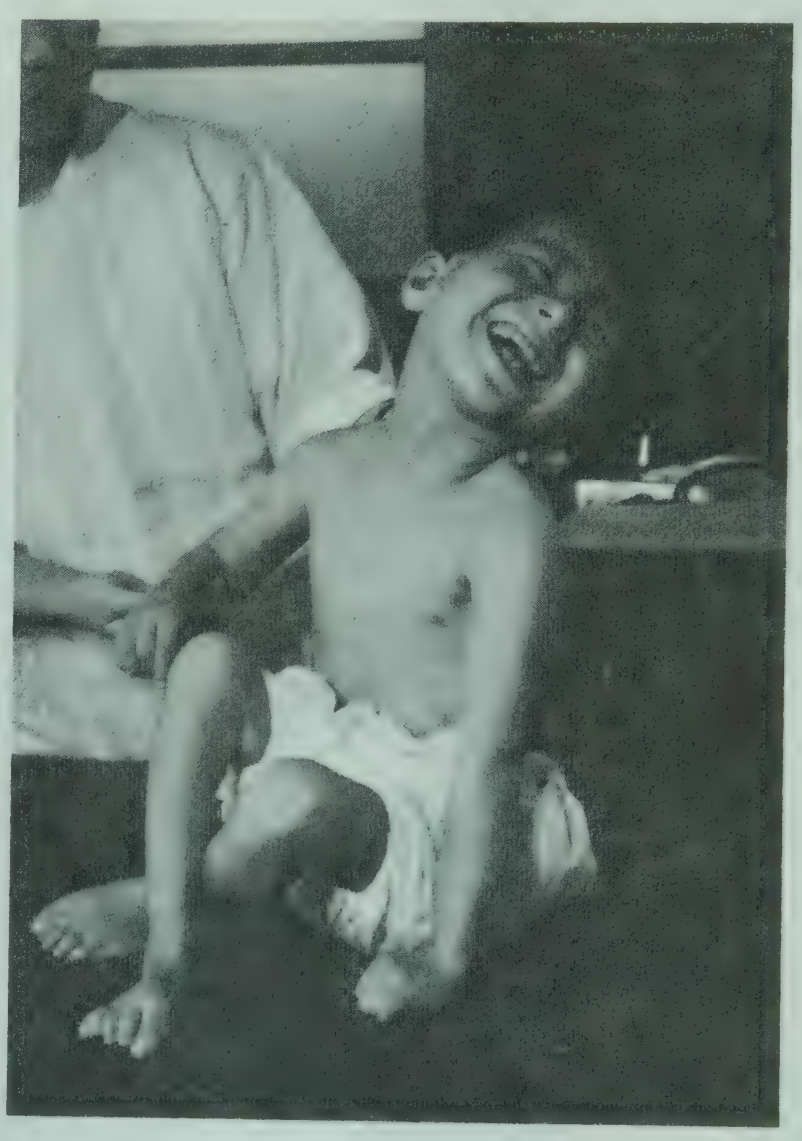

Fig. 4 Forced laughter, a condition resembling akinetic mutism. Female aged six years, born in 1956, died in 1977.

Compared with cases of cerebral palsy as a group caused by other factors, congenital Minamata disease cases exhibit a more marked degree of intelligence disturbance; cerebellar symptoms and strabismus are more common. Symptoms on the right and left side are undifferentiated, and no factors that might have caused abnormality were noticed during perinatal period.

Also, degenerative signs and malformations are rare, but microcephaly is observed in 60% of congenital Minamata disease cases. Abnormality of chromosomes has not yet been recognized.

During 15 years of follow up research,

improvement of motor function has been more noticeable in mild cases than in those of medium degree. Especially, paroxysmal symptoms, hypersalivation, primitive reflex and cerebellar symptoms have been relatively susceptible to improvement, and in some cases only clumsiness of movement remains apparent. But even in light cases, intelligence disturbance was left unimproved.

Pathology and experiment

General atrophy and hypoplasia of the brain cortex and abnormality of the cytoarchitecture, remaining matrix cells, hypoplasia of the corpus callosum, intramedullary preservation of the nerve cells, and dysmyelination of the pyramidal tract have been observed. In the cerebellum, hypoplasia of the granular cell layer and other layers as well as degeneration of granular cells (characteristic of Minamata disease) were observed (Matsumoto and Takeuchi, '65).

Researchers succeeded in causing brain disturbances in fetuses of pregnant cats or mice by giving methylmercury experimentally (Morikawa, '61; Moriyama, '67). Further, transplacental passage of organic mercury was confirmed by means of radioautography (Fujita, '69). The possibility of brain damage through mother's milk was also confirmed (Deshimaru, '69).

Epidemiology

In the diagnosis of congenital Minamata disease, epidemiological factors are very important. In the three most heavily contaminated areas, Yudo, Modo, and Tsukinoura, where are fishermen's villages of Minamata City, 220 infants were born during 1955 through 1958. Among them, 13 were suffering from severe congenital Minamata disease, and the morbidity rate was high at 6.9%. Incidence of infantile and adult cases coincided, both in region and time. Later research revealed that the disease existed in a broader region, and 40 cases have been officially registered until 1976. In many families, Minamata disease affected two or more members. However, the symptoms of mothers were relatively light. Of 28 affected mothers, all showed peripheral sensory disturbance, but such symptoms as mild incoordination (79%), constriction of the visual field (57%), dysarthria (43%) and tremor (39%) were not observed in all of the cases (Harada, '76). In Minamata cases, mercury values in the hair of the parents of affected infants was not known at time of birth, but two to five years afterward patients and their parents showed high level of mercury in the hair (Minamata Disease Study Group of M. D., '68). In the Niigata case, one mother showed 293 ppm of mercury in the hair during pregnancy. Also, a mother of a New Mexico case had a mercury value of 2.91 ppm in her blood, and her affected infant had 2.77 ppm in its urine. Therefore, for the diagnosis of congenital Minamata disease it is valuable that mercury contents in the hair, blood or urine were high in the postnatal period.

In cases at Minamata, methylmercury values in the umbilical cords of patients were more than 1.0 ppm in many cases (Harada, '76, '77).

Sometimes, the mercury value does not necessarily coincide with the usual clinical symptoms, but a correlation with the degree of environmental pollution is observed. Mental retardation (excluding cases of congenital Minamata disease) of children born between 1955 and 1958 in the heavily polluted Minamata area was 29.1%, and was 17.5% in pupils of lower secondary school in the Minamata area. Both figures were significantly higher than those of control areas. Furthermore, clumsiness in movements of fingers and other motor functions were seen in these mental retardation cases, and in these infants mild or incomplete cases of congenital Minamata disease are suspected (Hirada, '76).

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Japan Quarterly, 25 (1), 20–34 p. (January–March, 1978)

Minamata Disease as a Social and Medical Problem

Harada Masazumi

ON May 1 1956, Dr. Hosokawa Hajime, the head of the Chisso factory hospital at Minamata, reported to the Public Health Department: "An unclarified disease of the central nervous system has broken out." This is the official "discovery" date of what is now called Minamata Disease. During the twenty years that followed, the name "Minamata" became known throughout the world, and the worldwide interest in organic mercury poisoning produced some outstanding research results. In Japan, Minamata Disease brought unprecedented notoriety to environmental pollution and led to various environmentalist movements. However, what has been solved in connection with Minamata Disease?

As of November 1977, there were 1,255 officially verified patients, over 3,500 were applying for verification, and nearly 1,000 were left pending. Officials, companies and medical doctors know no means to cope with the situation. According to local government officials, it has been estimated that it would take five to thirty-two years to verify all the patients if they were dealt with at the present pace.

In December 1974, the patients finally filed a suit with the Kumamoto District Court against the governor of Kumamoto Prefecture, accusing him of unlawful administrative negligence in dealing with the patients' applications for verification.. In December 1976, the court gave a verdict that the administration should be held responsible for the delay in verification. This came after a court verdict in March 1973, at the conclusion of the first Minamata trial, holding the corporation responsible..

Meanwhile, the number of applicants continued to increase. There was a rumor that some were fake patients trying to get an indemnity, and words spoken by the chairman of the special committee for antipollution measures of the Kumamoto Prefectural Assembly resulted in the arrest of some patients on October 7 1975. Those applicants who were rejected by the Minamata Disease Verification Committee filed a damage suit against Chisso Corp., demanding that they be verified. As they raised objections to the committee's decisions, fierce arguments regarding "the picture of Minamata Disease" took place!

On the surface, these phenomena constitute the question of responsibility for the delay in verifications, and the problem seems to be one of setting up criteria for verification. However, this is only the tip of an iceberg. The more one studies the disease, the larger

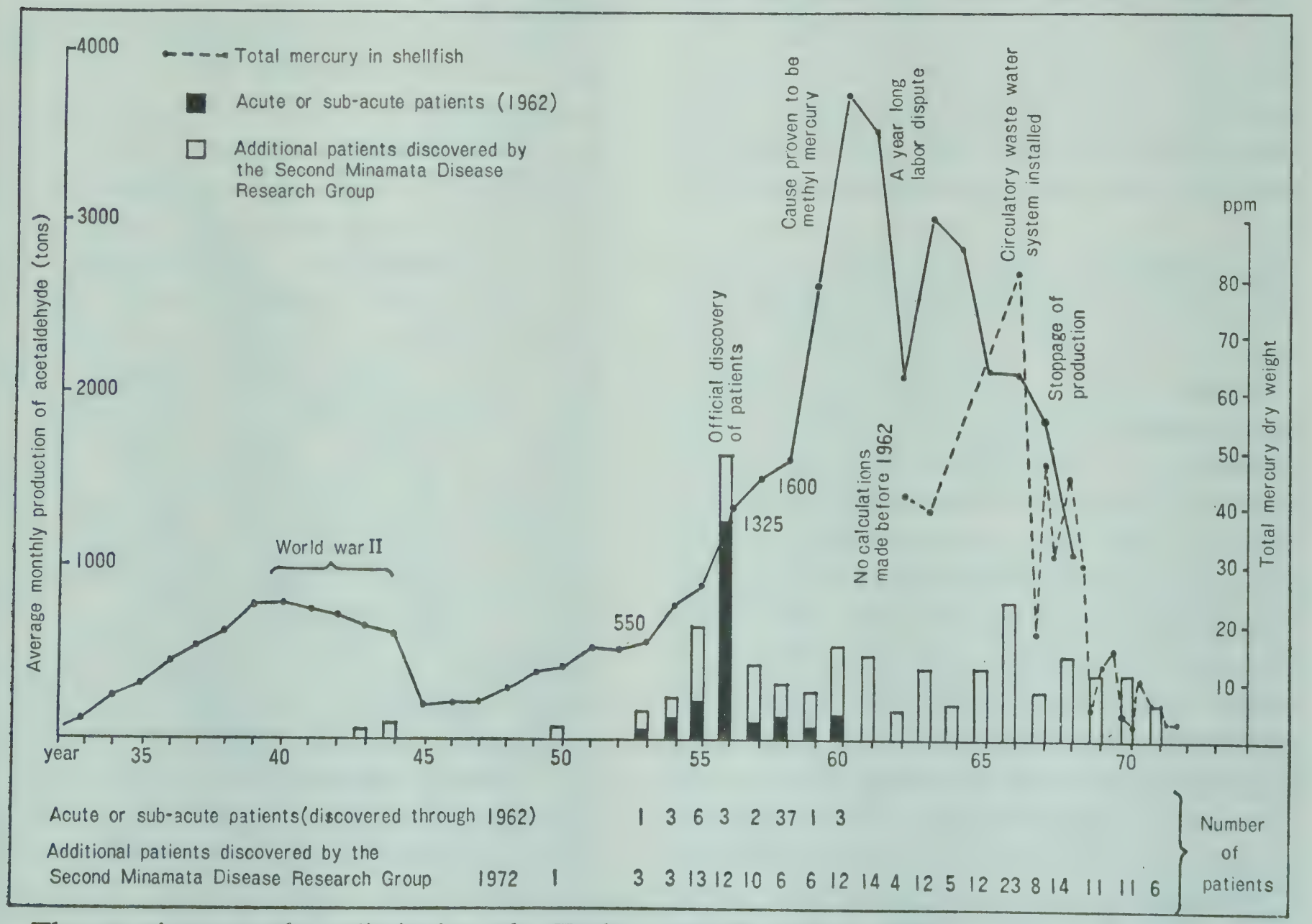
is the extent of damage that becomes known. Why did the damage spread to such an extent? Why has the actual situation not been made fully clear? Why has the number of applicants increased nearly twenty years after the discovery of the disease? What is the verification system in terms of medical science? What in fact is Minamata Disease? There is a huge pile of problems.

History

Since Minamata Disease is a type of poisoning caused by continuous environmental pollution, it did not occur suddenly. From 1918 Minamata Bay had been polluted, though on a small scale, by waste water from the Chisso Corporation's Minamata factory, containing, among other things, mercury. In 1925 Chisso compensated the local fishery cooperative because of a decrease in the catch caused by the waste water.[1,4] In view of the fact that the problem of pollution occurred often, it is clear that varying degrees of environmental pollution had existed prior to the discovery of Minamata Disease.

The pollution apparently became severe after 1950. Fish began to float on the surface of the sea and shellfish often perished. In 1953 cats went mad and died; they would suddenly jump up, whirl in violent circles, and die after hypersalivation and convulsions. Not only cats but also pigs, chickens and dogs died; even birds began to drop into the sea while flying. It is now clear that by that time the disease had broken out. Since this was before the discovery of the disease, such unusual changes in the ecological field were completely ignored.. Yet these changes

Figure 1. Comparative Chart of Acetaldehyde Production Rate, Onset of Minamata Disease, and Mercury Content in the Shellfish of Minamata Bay



These patients are those limited to the Tsukinoura, Detsuki and Yudo areas. Shellfish are Venus Japonica off Koiji Island (Fujiki)

were in fact a warning to humanity.

With the discovery of the disease by Dr. Hosokawa in May 1956, investigation began to show its cause. In August the waste water from the Chisso factory was already suspected. However, Chisso did not cooperate in the investigation, alleging a need to keep trade secrets, and production even increased rapidly (Figure 1).

Meanwhile, fishermen could no longer sell their catch, and a minimal standard of living was imposed on them. It was the most difficult and insecure period for both fishermen and patients. The social situation was such that the factory could not be told to stop pumping out the waste water. If the factory stopped emitting the waste water at this stage, the number of patients would have been kept at minimum. Furthermore, the Government was unable to ban fishing officially since the cause was still "unknown." The fishermen continued to fish as far as possible from the shore and continued to eat their catch. However, alerted by medical doctors and also on their own initiative, they refrained from eating fish and shellfish from the bay, and the number of new patients decreased temporarily.

In September 1958, however, with the expansion of production, Chisso diverted its mercury waste water to the mouth of the Minamata River.[1] Consequently, contamination spread throughout the Shiranui Sea (Figure 2). In April 1959, new patients were found in Izumi and Tsunagi outside Minamata, and cats were seen to go mad and die on the islands of Goshonoura, Shishijima and Nagashima located on the other side of the Shiranui Sea. Since Minamata Bay is a double bay, it had the natural function of preventing contamination from spreading; but the diversion of the waste water to the river spread contamination. By the time cats go mad and die, there is already an outbreak of the disease among human beings. This was confirmed in 1965 at Niigata; but medical examinations of the residents were not carried out.

By the summer of 1959, it was almost certain that Minamata Disease was caused by methyl mercury poisoning. And that October, Dr. Hosokawa proved that the acetaldehyde waste water fed directly to cats caused the same symptoms as Minamata Disease. This indisputable evidence, however, was never made public.[1] Even at this stage, if countermeasures had been taken—such as making the waste water completely safe, banning fishing, an appropriate fishery policy, aid for medical research on the disease and aid to the patients—contamination would not have spread and the damage would have been limited.

In 1960 a survey was carried out by Kumamoto and Kagoshima prefectures to determine the mercury content in the hair of fishermen living along the Shiranui Sea. The survey revealed that in spite of the lapse of

Figure 2.

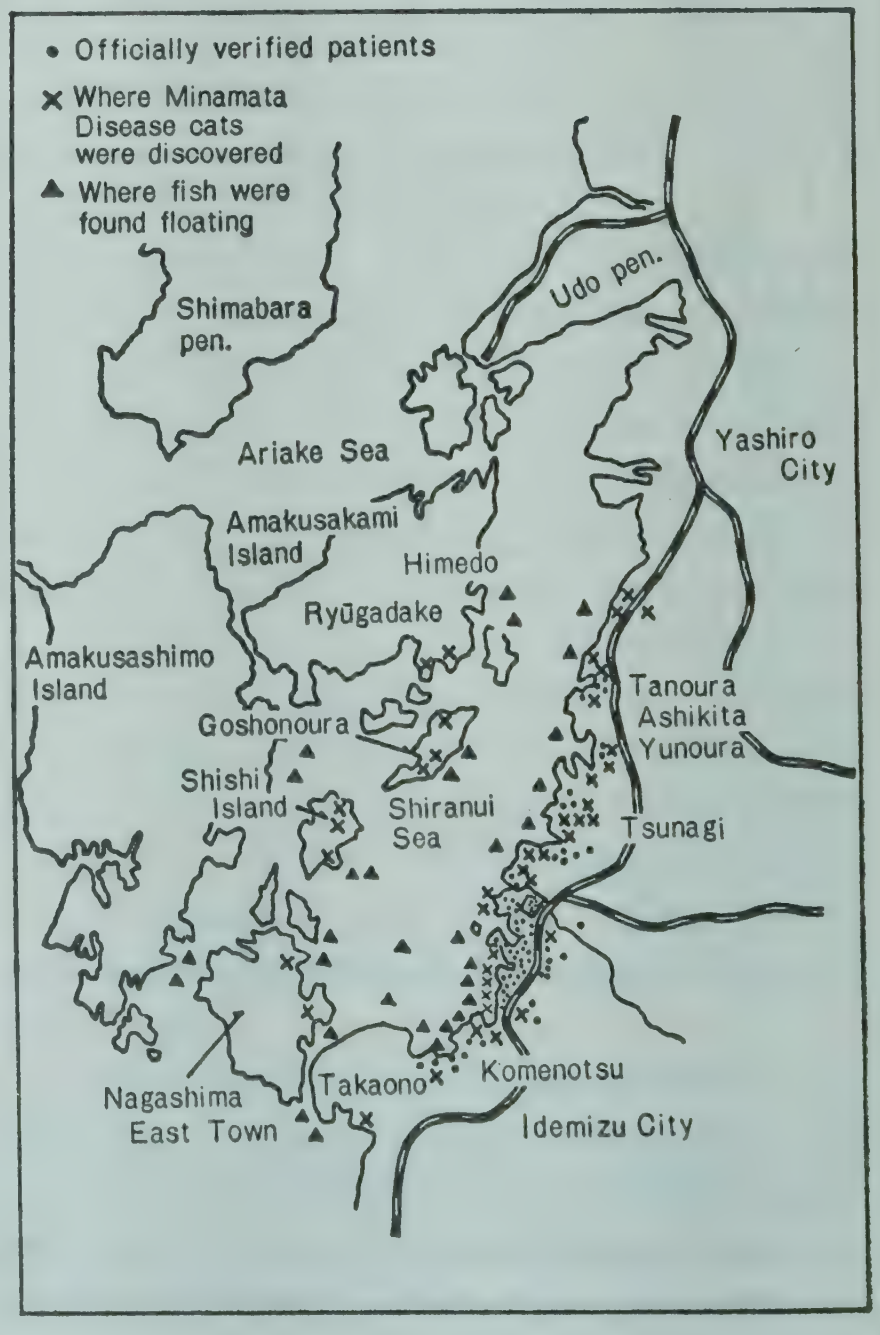


Table 1. Mercury Content in Hair of Healthy Fishermen, 1960

ppm	~1	1~10	10~50	50~100	100~150	150~200	200~300	300~	Total
Minamata	7	31	100	49	11	1			199
Tsunagi		12	61	23	4	2			102
Yunoura			14	9	1				24
Ashikita		1	19	19	1				40
Tanoura		6	15	11					33
Ryugatake	2	22	57	5		1			87
Goshonoura	6	53	334	75	11	1		2(357 920)	482

ppm	~20	20~50	50~100	100~200	200~300	300	Total
Komenotsu	185	117	105	37	5	1 (624)	445
Akune	26	4	1	3		1 (338)	33
Takaono	2	3	5				10
Higashi Town	18	32	23	2 (142)			75
Kumamoto City (control)	4 18	9	0	0 0	0	0	31

( )=ppm

three years after the discovery of the disease, contamination had spread as far as Goshonoura on the other side of the sea (Table 1). For instance, 920 ppm of mercury in hair was detected at Goshonoura. A field survey based on the mercury content in hair was then carried out together with medical examinations. The survey showed only three new cases of minor symptoms, so it was believed that the Minamata Disease was over. For the next ten years no follow-up survey was conducted though contamination continued, and because of the system of voluntary registration by patients themselves, Minamata Disease did not come to the surface.

After the discovery of Minamata Disease in 1956, sales of fish fell drastically, and many of the local residents were driven out of Minamata because of poverty. A Mr. Kaneko was found in a survey to have mercury content of 100 ppm in his hair. He did not have a medical examination because his family begged him not to.[1] A Mr. Shibata was a typically acute case with serious symptoms such as dysarthria, hypersalivation, ataxia and disturbance of vision. He was once confined to the City Hospital. But senior members of the local fishermen's association, suspecting the disease, took him out of the hospital, because the occurrence of a new case would be disastrous to them. Since he died at home, his name would not be included in the list of Minamata patients.[1] There were many patients in this category. At that time, senior members of the fishermen's association went round to both patients and doctors and asked them not to use the term Minamata Disease.

Table 1, giving data for mercury content in hair, is far from comprehensive because the survey was conducted in such a social situation. Yet the table shows clearly that the whole area of the Shiranui Sea was contaminated. There were 200,000 people living along the coast at that time, and at least 100,000 were exposed continuously to heavy contamination (Figure 2). A survey should have been conducted then to find out how these people were being affected; but nothing was done for the next ten years.

Contamination at that time was extremely heavy. For instance, a cat taken from Kumamoto City to Minamata, was taken ill on the 30th day.[6] In an experiment, it would

require 1 mg/kg of methyl mercury a day to cause the same symptoms as Minamata Disease in a cat in 30 days. Judging from these facts, one can detect the extent of contamination to which the local residents were continuously exposed.

When the 1960 survey was conducted, a fisherman named Matsuda, whose two children were already suffering from Minamata Disease, was found to have dysarthria, constriction of the visual field and sensory disturbance. However, though handicapped, he was still fishing. The doctor who examined him told him that if he continued to eat fish he would develop Minamata Disease, and left. This episode is interesting because it shows the criterion for diagnosing Minamata Disease at that time. The fisherman's condition did deteriorate later, and soon he was bedridden. Two years later he died. However, the cause of his death was diagnosed as softening of the brain. His family, already having two Minamata Disease patients, thought that "it would bring disgrace upon the family to have yet another patient."

Thus the myth that the "Minamata Disease was over in 1960" spread, and the doctors who examined the patients kept silent. Some doctors did so intentionally; but many did so because they really had a preconception that the disease had been "concluded." Because they saw a number of typically acute cases at the beginning, they built up a static picture of Minamata Disease, as illustrated by the above episode. When some suspected cases were referred to a university hospital, they were sent home, often with three or four diagnoses other than that of Minamata Disease. Those at universities, too, were unaware of the actual conditions. Meanwhile, Minamata Disease was changing from acute or sub-acute to chronic poisoning.

Clinical Toxicology

Minamata Disease is methyl mercury poisoning.[7] One of the important references which led to the discovery of its cause was a paper by D. Hunter and D.S. Russell.[8,9] The paper carried descriptions of cases of methyl mercury poisoning of workers in a factory producing methyl mercury. The clinical and pathological findings in these cases coincided with those of Minamata Disease. It is clear that occupational poisoning provides an important guide for the investigation into the cause of an environmental disease. However, there is a decisive difference between the two types of poisoning as they occur under different conditions. This difference is important in understanding Minamata Disease.

Our knowledge of organic mercury poisoning prior to the outbreak of Minamata Disease concerned only occupational poisoning through direct exposure. In other words, occupational poisoning is direct poisoning of workers which occurs under a certain conditions, whereas Minamata Disease is poisoning of the entire population of a contaminated area, including embryos, the aged and those who are already ill. Furthermore, it is indirect poisoning through the food chain with environmental pollution as its medium.

When these points are considered, it becomes clear that although Minamata Disease and occupational poisoning coincide with each other in some respects they do not in others. Further, though they are caused by the same substance, their clinical symptoms differ, depending on whether the poisoning is acute, sub-acute or chronic. Poisoning affects the human body differently under different conditions—in terms of the poisoning process (oral or tracheal), the amount of poison, and the length of exposure to it. The effects may appear to be symptoms of a completely different disease.

Let us look at a case of carbonic disulfide poisoning. In a case of heavy exposure, disturbance of consciousness, a psychotic state, or dementia may appear (Table 2). If exposure is less, a neurasthenia state and polyneuritis may occur. If the first case is called either acute or sub-acute poisoning,

Table 2. Carbon Disulfate Poisoning

	1926	1935–44	1945–54	1955–64	1965–74
Concentration	>100 ppm	>50 ppm	>20 ppm	20< ppm	20< ppm
Symptoms	disturbance of consciousness, convulsions, Korsakow's syndrome, psychosis.	polyneuropathy neurasthenic state.	hypochondria neurosis.	hemiplegia dementia.	disturbance of circulation of the brain.
Types	acute or sub-acute poisoning	chronic poisoning	incomplete poisoning	nonspecific poisoning	slight and long-period poisoning

the second one may be termed chronic poisoning. If exposure is light, subjective symptoms such as headache and scotoma are the main symptoms, and they might be taken for those of neurosis or hypochondria. However, if the exposure continues, symptoms of a nonspecific disease such as nephritis, nephrosis, or hypertension may be observed.

Thus in the case of a nonspecific disease, individual symptoms do not show whether the case is CS^2 poisoning or not. In such a case, epidemiological consideration is necessary for a diagnosis: that is, a group of contaminated workers should be compared with a control group with the goal of determining the deviation in terms of harm to health. The CS^2 poisoning discovered in this way was not over. It has been discovered that if light exposure continues for a long period of time, it causes, together with the individual factor of sclerosis of the blood vessels from aging, encephal ovasculopathia suffocarbonica chronica. CS^2 poisoning is one of the relatively well-known types of poisoning.[10] It also has been shown that poisoning itself causes extremely varied harm to health.

If we consider this lesson in connection with Minamata Disease, we learn that until

Table 3. Clinical Symptoms in 35 Cases of Acute and Sub-Acute Minamata Disease

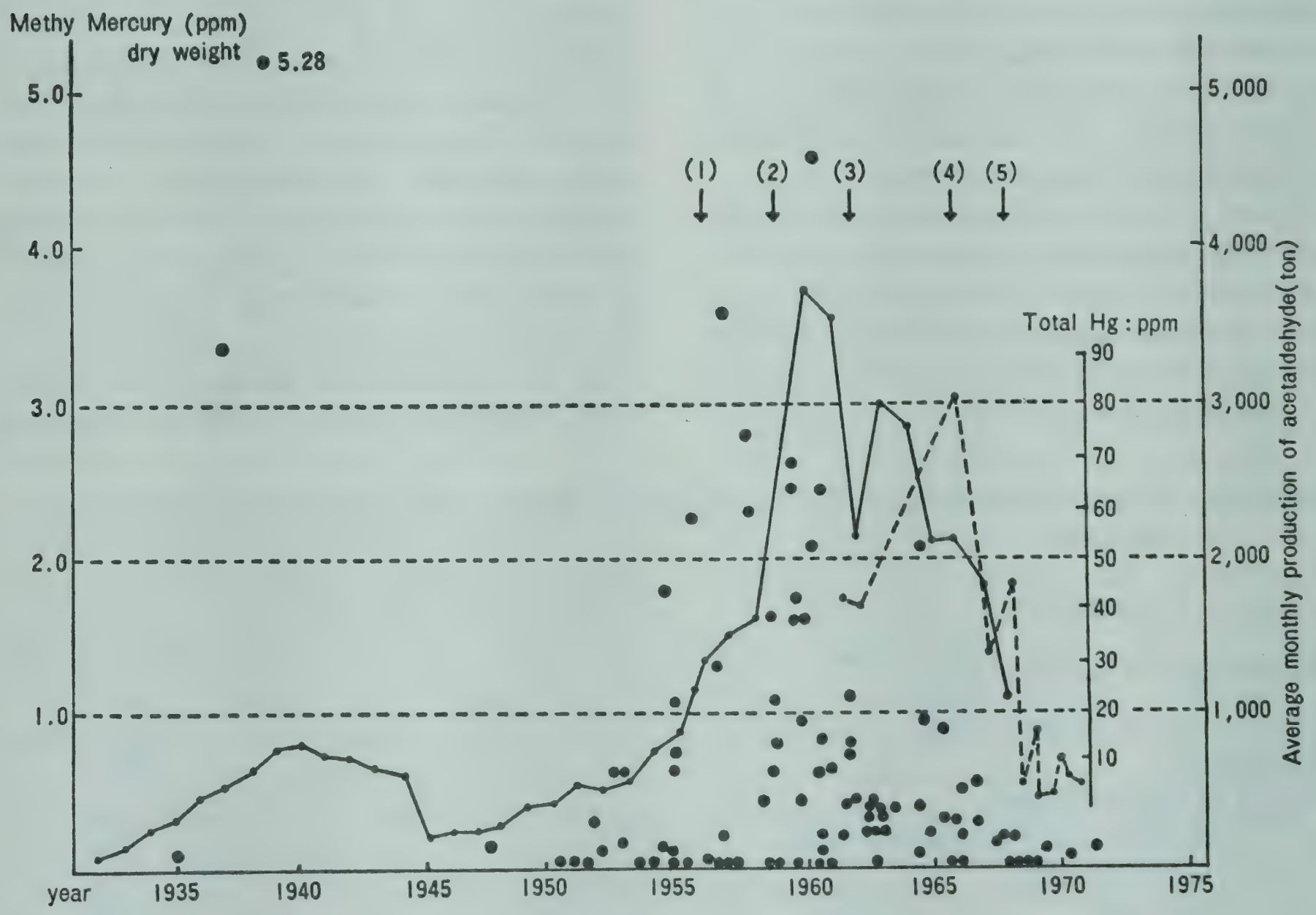
Symptoms	%
Disturbance of sensation {Superficial	100
Disturbance of sensation {Deep	100
Constriction of the visual field	100
Dysarthria	88.2
Ataxia {adiadochokinesis	93.5
Ataxia {in finger-finger, finger-nose tests	80.6
Ataxia {Romberg's sign	42.9
Ataxia {ataxic gait	82.4
Impairment of Hearing	85.3
Tremor	75.8
Tendon Reflex {exaggerated	38.2
Tendon Reflex {weak	8.8
Pathological Reflexes	11.8
Salivation	23.5
Mental disturbances	70.6

(H. Tokuomi, 1959)

about 1960 what we thought of as Minamata Disease was limited to typical cases of acute and sub-acute types. The frequency of clinical symptoms showed that these cases were typical examples of only acute and sub-acute types (Table 3). Thus the fact that 16 patients died within three months after falling ill, six within six months, and one within one year shows that these patients suffered from acute and serious poisoning. Therefore, in reflection we later defined Minamata Disease as "every type of physical destruction caused by methyl mercury poisoning through environmental pollution extending from the past to future."

The physical destruction of the population brought about by Minamata Disease was something that humanity had never experienced. The only other occurrence in the past comparable to it was radioactive contamination from atomic bombs. Therefore, the medical doctors at that time lacked a visual point based on realization of the actual situation. That is why there are still social and

Figure 3. Comparative Chart of Acetaldehyde Production Rate, Methyl Mercury in Umbillical Cords, and Mercury in the Shellfish of Minamata Bay



—— Average monthly production of acetaldehyde (ton)
..... Mercury content in the shellfish (ppm) dry weight
● Month of childbirth and methyl mercury content (ppm) dry weight
(1) Official discovery of patients
(2) Cause proven to be methyl mercury
(3) Production decrease owing to a year long labor dispute
(4) Circulatory waste water system installed
(5) Stoppage of production

Table 4. Acetaldehyde Producing Plants

Companies	Plants	Prefecture	Production start	Production stoppage	Acetaldehyde Produced (in thousand tons)	Mercury Recovered (in tons)
Chisso	Minamata	Kumamoto	1932	1968	456	207
Denka Kōgyō	Ōmi	Niigata	1945	1968	167	54
Shōwa Denkō	Shikase	Niigata	1936	1965	103	34
Tekkōsha	Sakata	Yamagata	1939	1964	35	13
Nihon Gōsei	Ōgaki	Gifu	1928	1964	150	8
Nihon Gōsei	Kumamoto	Kumamoto	1944	1965	96	5
Daiseru	Arai	Niigata	1937	1968	307	5
Mitsubishi Gas	Hamamatsu	Niigata	1960	1965	38	26

medical problems related to Minamata Disease.

As the damage caused by Minamata Disease was minimized Chisso continued to pollute the area. In 1962, Prof. Irukayama proved that the factory process producing acetaldehyde had methylated the inorganic mercury[7]; but production expanded and contamination of Minamata Bay continued. Shellfish in the bay showed high mercury content until May 1968 when the production of acetaldehyde stopped. Such a relationship also existed in the human body. Figure 3 shows the mercury content in umbilical cords, kept in a dried state, of residents of the Minamata area. Acetaldehyde production corresponds remarkably well to mercury levels in umbilical cords.[11,12]

Of course, one cannot say that Chisso did not take any measures. In June 1966, it switched to closed cycling system drainage. However, it was too late. The delay on the part of Chisso in taking countermeasures was related to the fact that after 1960 the occurrence of the disease was hidden. Publicity was skillfully given to the premature conclusion that the "Minamata Disease is over," and the fishermen, who had been refraining on their own initiative from catching fish in Minamata Bay, began after 1960 to move back to the fishing grounds near the bay. Those impoverished fishermen had no alternative but to continue to eat fish. Some of the old people would not believe until the end that fish were the cause of poisoning.

Under such circumstances chronic cases of Minamata Disease occurred one after another. However, because the definition of Minamata Disease included only acute and typical cases, those chronic cases were regarded as other diseases and discarded, and nothing was done for the next ten years.

Latent Minamata Disease

In September 1968, the Government issued its first statement on Minamata Disease: "Minamata Disease was caused by a methyl mercury compound produced in the manufacturing process of acetaldehyde at the Minamata factory of Chisso." By that time, however, all of the plants in Japan manufacturing acetaldehyde using mercury as a catalyst had ceased to operate (Table 4). It seems that the Government had been concerned about the possible adverse effects on those plants in operation. Among those listed in Table 4, Shōwa Denkō created the second Minamata Disease and Nihon Gōsei the third.

The official designation of Minamata Disease as an environmental disease resulted in an unexpected development. On June 14 1969, the patients filed a damage suit against Chisso. They broke their silence and began to tell the truth. Thus those medical researchers, doctors and administrators who

had concluded that the "Minamata Disease is over" began to be denounced. In May 1969, Prof. T. Takeuchi discovered during an autopsy that the brain of a patient, though he was not classified as a Minamata Disease patient, had been affected by methyl mercury. Prof. Takeuchi called the disease "concealed Minamata Disease." In June of the same year, the present writer suggested that "the full extent of the damage should be brought to light as verified cases form only the tip of an iceberg," and latent Minamata Disease should be called "hidden Minamata Disease."[14]

Though the residents repeated their request for a mass examination, the administrative authorities did not meet their request stating the "Minamata Disease is over. Since no new patients have registered, it is not necessary to carry out a mass examination."[1]

The trouble was that only the Minamata Disease Verification Committee had the power to diagnose cases of the disease and its concept of the disease was very limited. The concept was extremely rigid regarding not only possible combinations of symptoms but also areas of occurrence and dates of falling ill. Consequently those who came forward at great pain were often not diagnosed as Minamata Disease patients. When we explain the problem of Minamata Disease we cannot ignore that thorny system of verification.

If we realize that Minamata Disease is poisoning of the entire population caused by environmental pollution, we cannot draw a distinction between typically acute cases and healthy persons. This holds especially true when we look at it from the medical standpoint of pursuing every effect of methyl mercury on the contaminated residents. For instance, it does not stand to reason to say that the case is Minamata Disease if there are five symptoms but not with four symptoms. However, the criteria adopted by the committee were: (1) whether the patient required medical aid; (2) whether the patient was qualified to receive compensation from Chisso. This system of verification indeed distorted the clinical picture of Minamata Disease.

After the official discovery of Minamata Disease in May 1956, the local medical association, the Chisso factory hospital, the City Hospital and doctors at health centers formed the Committee to Take Countermeasures Against Minamata Disease, and they took part in the investigation of the cause. Through various surveys and reports by the home doctors, new patients were found one after another, and the information and data kept by the doctors led to discovery of the disease among the diseased patients. These surveys were not adequate by present-day standards. However, when neither the cause nor the clinical picture of the disease was known, the surveys were the best that could be expected at that time.[1]

In November 1969, the Minamata Disease Committee at the Ministry of Health and Welfare reported that "the cause of Minamata Disease is an organic mercury compound in fish and shellfish." The patients began a sit-down demonstration at the main gate of Chisso demanding compensation and suspension of discharge of the waste water. There also was a move around that time to set up a special committee for verification of Minamata Disease. On December 25 1969, the Council for Verification of Minamata Disease was formed. It is clear that there was some connection between the council and an agreement on compensation reached five days later by Chisso and the patients.

The chief of the Health Department of Kumamoto Prefecture at that time explained: "It has been decided to set up an official organ in view of the possibility of treating the patients at national expense and the problem of compensation." Furthermore, he told the patients: "We need an authoritative organ which can verify the cases of Minamata Disease. The company will not agree to compensate if a case is verified by only one

doctor." An agreement signed on December 30 1969, used the word "verification" for the first time: "... regarding the new patients (verified by the committee) after the signing of the agreement ..." It is clear that the main function of the committee was to find out whether the patient was qualified for compensation. In fact, whenever a new case of a verified patient occurred, it was reported officially to Chisso.

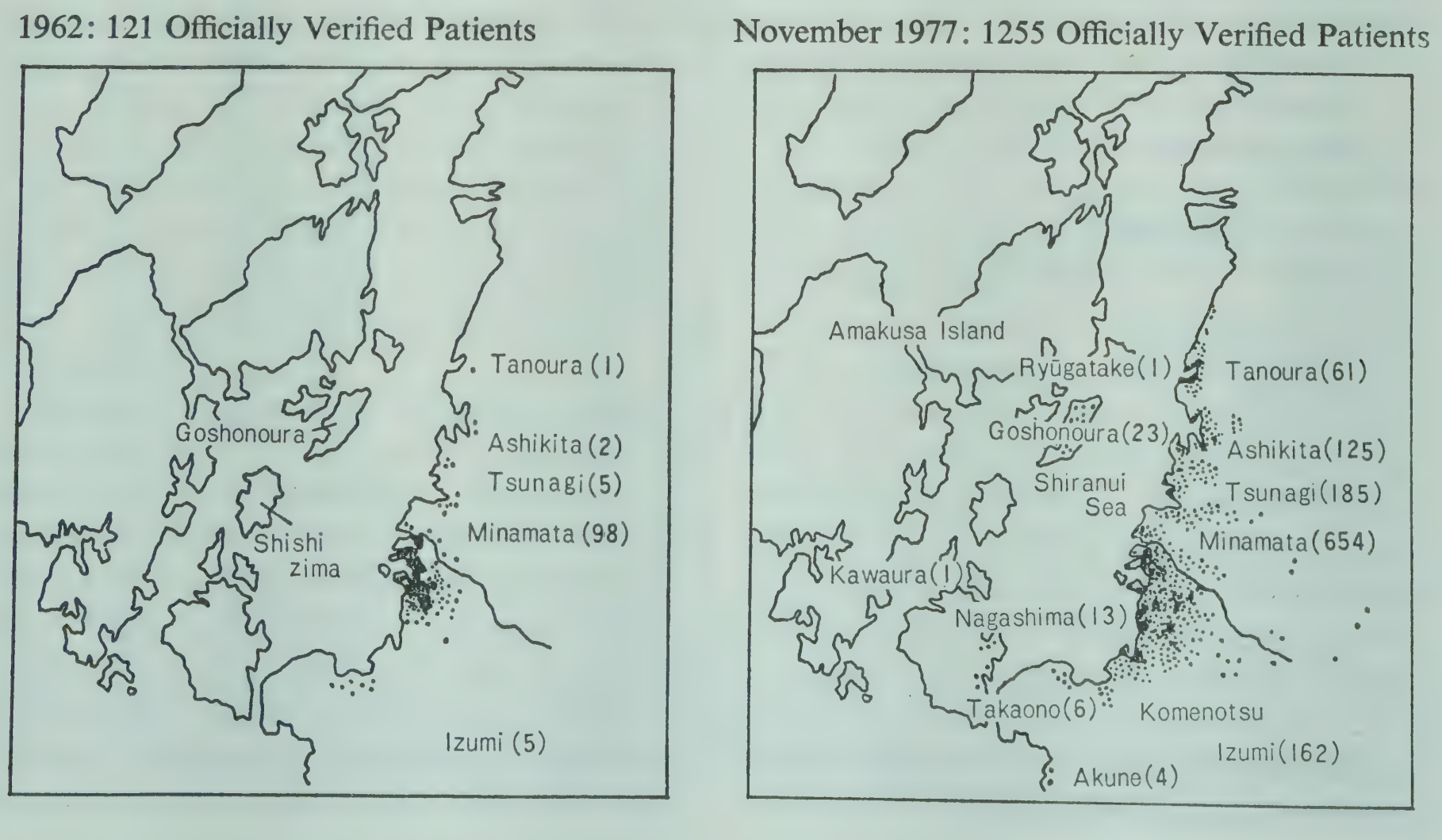
Though the committee was reorganized in March 1964 and again in December 1969, it seemed to have retained its character. Between 1960 and 1970, 37 cases were verified. However, since 22 of them were newly found congenital Minamata Disease cases, verification was apparently a limited chance for the patients. In 1970, for instance, 11 of 32 patients who applied for verification were turned down. These patients were dissatisfied with the committee's decisions and appealed to the authorities.

In August 1971, the Environment Agency, after investigation, accepted the patients' claims entirely and overruled the committee's decisions, issuing the following recommendations: (1) The committee's decisions should be made independently of the problem of compensation. (2) Whether or not the case is serious is not the point in considering the effects of organic mercury (even in a mild case, if the patient is affected by organic mercury, it is Minamata Disease). (3) Importance should be attached to epidemiology. (4) Even if there is a complication, if the effects of mercury cannot be denied, the case should be included as Minamata Disease.

The decision by the agency seemed to produce a broader clinical picture of Minamata Disease than before. The number of patients verified rose to 583 between 1971 and 1973 (Figure 4). However, the number of patients verified was still limited as the system of verification depended on the patients' own application. For those patients living in Chisso-controlled areas, applying for verification required considerable courage, and fishermen who were afraid of not being able to sell fish again did not apply.

Meanwhile, the agency's decision was misinterpreted by the general public as a decision to "help the doubtful." Con-

Figure 4. Increase of Verified Patients



sequently, the patients verified after the decision were considered "doubtful patients" and were distinguished from those in the past. Thus they were discriminated against as "new and therefore fake patients." Although they were atypical, incomplete, and mild cases, they were, medically speaking, chronic patients who were undoubtedly harmed by methyl mercury. Yet even some doctors could not believe that the newly verified patients were Minamata Disease cases in medical terms.

Clinical Symptoms of Minamata Disease

As has been described in connection with the system of verification, historically we had only a fixed view of Minamata Disease. Actually we should have tried to grasp the actual conditions harming the health of contaminated residents. Since there had been no "Minamata Disease" in the past, the clinical picture of the disease had to be established from the symptoms of the contaminated residents of Minamata. In 1973 a proper health survey of residents was at last carried out. The results showed, if we take only neurological symptoms, that nearly 30 percent of the residents (not verified yet) of the surveyed district had symptoms of M.D. (Table 5).[4] Further, it became clear that even in the Goshonoura district, where there were supposed to be no cases except those of cats, there were patients. In view of the fact that the survey covered only part of the total contaminated area, the number of patients would have been larger if it had covered a wider area. This was the situation after ten years of neglect.

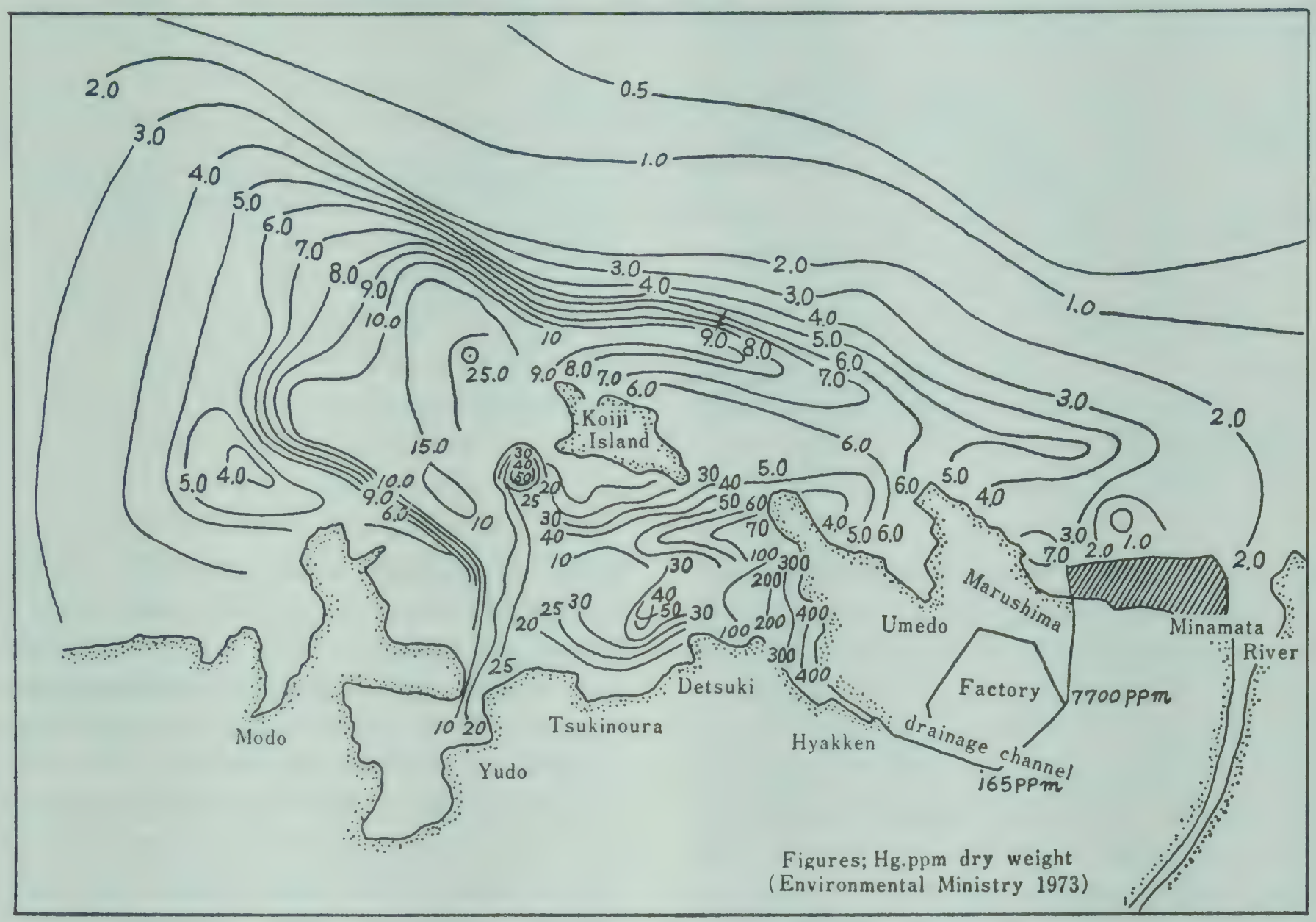
Strictly speaking, most of the patients

Table 5. Frequency of Neurological Symptoms in Inhabitants of Minamata, Goshonoura and Ariake Area, 1973 (Second Minamata Disease Research Group)

	Minamata (Tsukinoura, Yudo, Modo)	Goshonoura	Ariake (control)
Sensory disturbance	260 (28.0)	132 (7.6)	94 (10.3)
Incoordination (Total)	228 (24.7)	193 (11.2)	122 (13.4)
Ataxic gait	84 (9.0)	50 (2.9)	20 (2.2)
Adiadochokinesia	171 (18.4)	101 (5.8)	50 (5.5)
Finger-nose test	106 (11.4)	28 (1.6)	11 (1.2)
Dysarthria	114 (12.2)	63 (3.6)	18 (1.9)
Auditory disturbance	272 (29.2)	156 (9.0)	135 (14.9)
Constriction of the visual field	127 (13.7)	47 (2.7)	9 (0.9)
Tremor	94 (10.1)	87 (5.0)	27 (2.9)
Pathologic reflexes	56 (6.0)	34 (1.9)	21 (2.3)
Hemiplegia	17 (1.8)	9 (0.5)	10 (1.1)
Pain (limbs)	128 (13.7)	92 (5.3)	74 (8.1)
Epileptic seizure	26 (2.8)	19 (1.1)	8 (0.8)
Muscular atrophy	55 (5.9)	13 (0.7)	7 (0.8)
Parkinsonismus	23 (2.5)	13 (0.7)	7 (0.8)
Deformities of limbs	81 (8.7)	104 (6.0)	73 (7.8)
Intelligence disturbance	211 (22.7)	178 (10.3)	98 (10.8)
Hypertension	218 (23.4)	237 (27.5)	180 (19.1)
Total	928 (100.0)	1,723 (100.0)	904 (100.0)

Minamata percentages exclude the 3.9 percent of patients already verified in the Tsukinoura ,Yudo, and Modo areas of Minamata.

Figure 5. Recent Mercury Content of the Mud at the Bottom of Minamata Bay



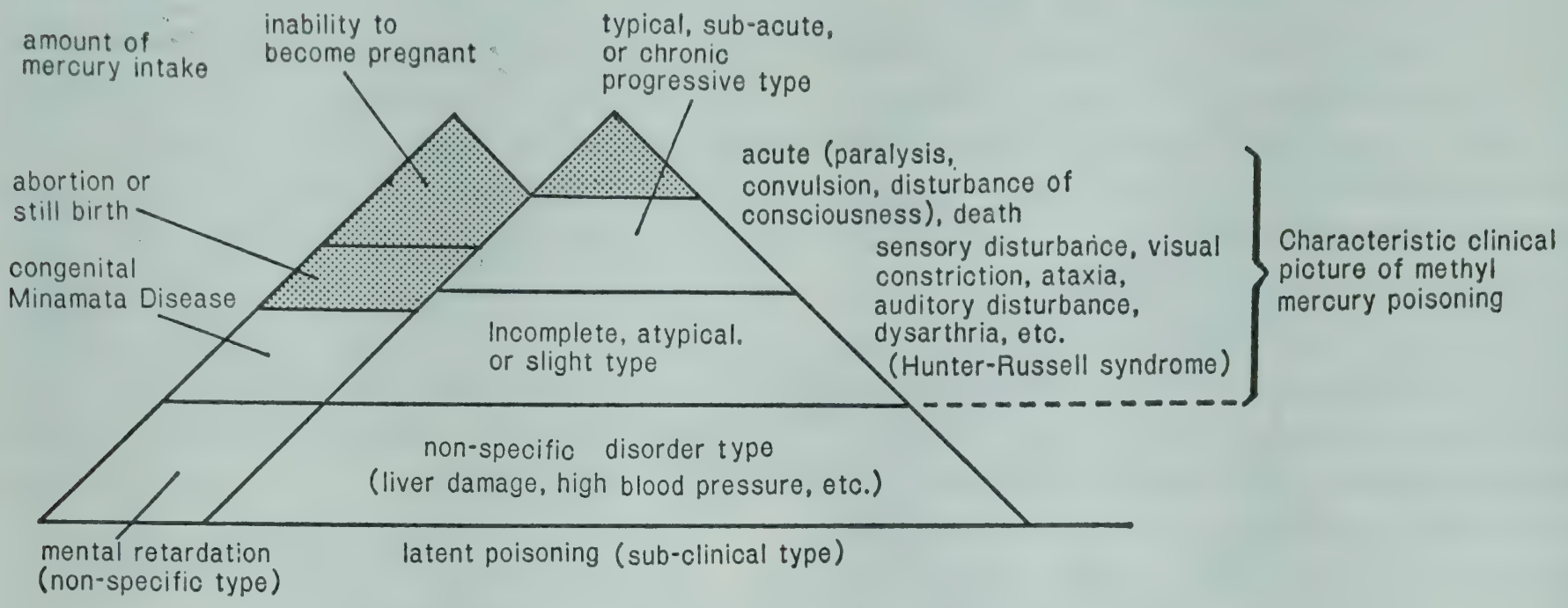
known at present have not fallen ill recently. In most cases the patients fell ill more than ten years ago. But what is significant is the fact that contamination has continued until today (Figure 5). Further, the symptoms of the patients are advancing, though slowly. It is not possible to determine whether the chronic Minamata Disease is caused by long-term, low-level poisoning or by the delayed effects of residual mercury, or by aging, or by complications.[4]

From the viewpoint of clinical toxicology, we cannot limit the symptoms of Minamata Disease to neurological ones. Figure 6 is a diagram of the relationship between methyl mercury contamination and Minamata Disease. In the case of sudden high-level methyl mercury contamination, it results in acute, wide-ranging brain disturbance including paralysis, convulsions, disturbance of consciousness, and finally death. In this type, the symptoms peculiar to Minamata Disease are difficult to detect, and a case is similar to one of encephalitis. In a slightly less serious case, the classical Hunter-Russell syndrome will appear.[7,8]

In a case of lower-level or long-term contamination, the symptoms vary, and the disease appears as an incomplete type, or a slight type, or an atypical case. Further, in a case of low-level contamination, those neurological symptoms peculiar to the disease may not be clear, and a nonspecific disease such as heart, stomach, liver trouble or arterial sclerosis may be suspected. Although chronic Minamata Disease is being investigated, the research so far has touched only the tip of an iceberg.

Let us now consider congenital Minamata Disease. If a woman is acutely ill with the disease, she does not become pregnant. In a less serious case, a miscarriage or stillbirth

Figure 6. Relationship of Methyl Mercury Intake and Symptoms


amount of mercury intake
inability to become pregnant
typical, sub-acute, or chronic progressive type
acute (paralysis, convulsion, disturbance of consciousness), death
abortion or still birth
congenital Minamata Disease
sensory disturbance, visual constriction, ataxia, auditory disturbance, dysarthria, etc. (Hunter-Russell syndrome)
Characteristic clinical picture of methyl mercury poisoning
Incomplete, atypical, or slight type
non-specific disorder type
(liver damage, high blood pressure, etc.)
mental retardation (non-specific type)
latent poisoning (sub-clinical type)

will occur. What is diagnosed as congenital Minamata Disease at present is a case in which the level of contamination is such that the mother does not lose her generative function and the child is born alive. In an even slighter case, it may appear as mental retardation. Because congenital Minamata Disease has been confined to the cerebral palsy type, patients of the mental retardation type are not being treated as Minamata Disease patients as such.

Furthermore, since Minamata Disease is caused by contamination of an area as a whole including all of the inhabitants and families, there are naturally those who are already ill from other diseases. But the existence of other ailments such as senility, hypertension spondylosis deformans, or diabetes, does not mean there are no effects of methyl mercury. In other words, a traditional diagnosis is not absolutely effective in such a case. Rather, it is necessary to pursue the relationship between methyl mercury and other diseases. We have said repeatedly that "Minamata Disease should be regarded as a general disease." Recently a few reports have appeared on systemic diseases caused by mercury poisoning—poor metabolism, circulatory trouble, B^2-microgloblin, etc.

At Minamata and Niigata, first cats went mad and died, followed by a widespread outbreak of instances of severe brain damage symptoms, which led to the discovery of Minamata Disease. This is the typical pattern of discovery of an environmental disease. However, it is not effective if the pollutant is an unknown substance, if it is multiple contamination, or if it is low-level contamination. Furthermore, it is important to remember that by the time typical severe cases are discovered there will be many times as many patients as the serious cases.

The other method is to carry out a health survey of residents of a contaminated area and discover the deviation. This method is indispensable in the case of long-term, low-level contamination or multiple contamination. It is meaningless to deny the effects of contamination, discarding two or three atypical symptoms.

Environmental diseases in the future will be different from those at Minamata or Niigata; one finds examples in Canada and Sweden where mild or incomplete cases are the problems.[16,17] The present research on possible effects on the human body has an important bearing on the study of future environmental diseases. Especially the fact that in a mother the disease can affect the brain of the embryo without showing severe symptoms is a gravely important factor in considering the future of humanity.

Future Problems

The present problems relating to Minamata Disease lie in its 20-year history. What is in question is what has been achieved by medical science, by the company, or by the Government in the last twenty years.

Firstly, prompt assistance should be given to the victims. In science there always exists an unknown part; but this should not be used as an excuse for inadequate assistance to the victims. The system of verification which stubbornly looks for only those points which are 100 percent certain should be reformed. As long as one can establish the facts that there is contamination and that the patient's health is harmed, prompt assistance should be given to the patient. It can no longer be called assistance if the patient has to wait for five years for verification or if the case is verified only after an autopsy.

Secondly, medical research for the patients should be pushed forward. During the 20-year history of the Minamata Disease, medical science gave the patients the impression that it had abandoned them, and only acquired their distrust. Even the achievements made by medical science in pursuing the cause immediately after the outbreak have diminished. To regain the patients' confidence, medical science should perform its original function. For that purpose it should carry out thorough investigation of the extent to which methyl mercury, which contaminated the entire area of the Shiranui Sea, has affected the inhabitants without being disturbed by the question of verification. There, medical science will find a pile of problems which it should investigate, and its achievements are eagerly awaited by the world.

Without obtaining a clear clinical picture of the Minamata Disease, and without knowing the exact number of patients, it is impossible to take countermeasures. Since Minamata Disease destroys the health of all of the inhabitants, medical treatment should be developed with that realization. Therefore, a search should be made for medical treatment linked to the area, and participation by the patients in the treatment should be considered. The patients should not just be confined to a hospital. Medical science should find ways in which it can help the patients who wish to live fully as human beings in the area.

Thirdly, the environment should be restored. The Shiranui Sea, which has been widely and heavily contaminated, should be restored to its original state. This does not mean simply that the heavily contaminated area should be reclaimed. Restoration should be carried out in many fields—marine life, fishing, the depopulated islands, the local community which disintegrated over the period of 20 years, cultural and educational problems, and the feelings of the local inhabitants. For such overall restoration, Minamata Disease should not be confined to a narrow field of medical science. Medical science should work together with other disciplines such as natural sciences and social sciences, and the Government should adopt their achievements and recommendations. That is the only way in which government and science can serve living people and in which science can compensate the victims of the gigantic experiment. Of course it will not be easy to solve all these problems, but we have to accomplish the task: for there are similar problems, although the extent varies, both in Japan and in the world, and the problem of Minamata Disease is being viewed as a lesson for mankind.

Notes

1. Harada Masazumi: *Minamata Byō* (Minamata Disease). Iwanami-shoten, 1972.
2. On December 13 1974, 406 patients applying for verification filed an administrative suit against Kumamoto Prefecture, pleading that the delay in verification was due to negligence by the local government. Documents on "Negligence Trial."

3. On June 14 1969, 112 patients filed a suit against Chisso, demanding a total sum of ¥642,390,000 in damages. In March 1973, the Kumamoto District Court gave a verdict that Chisso should pay ¥16,000,000 to ¥18,000,000 per person.
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Effects of Tiopronin and Spironolactone in the Treatment of Chronic Methyl Mercury Poisoning

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Introduction

Industrial effluent contaminated with methyl mercury has been discharged into waterways of the Minamata area, causing pollusion of the sea. In 1956 a large number of residents in this district were found to have been poisoned by methyl mercury as the result of eating fish and shellfish polluted with this compound (1–7). In the first four years 121 patients were diagnosed as having severe and acute or subacute types of Minamata disease (1, 2). The consumption of fish and shellfish from the sea has temporarily prohibited, but the industrial plant using the acetaldehyde process which was the source of the pollution, continued to be operated in this way until 1968 (6, 7). Because of incomplete protective measures, the seas adjacent to this district are still polluted. In 1973, the eating of fish and shellfish taken in this area was again prohibited. However, subsequent clinical investigation of the residents revealed the presence of a large number of patients suffering from chronic Minamata disease. As of November 1977, 1,255 chronic Minamata disease patients had been officially verified. Over 3,500 had applied for verification, and nearly 1,000 cases were left pending (7).

In 1956, more than 100,000 residents of the Shiranui Sea district around Minamata Bay, mainly fishermen and their families, were considered to be suffering from methyl mercury poisoning. As contamination had been continuous over a period of more than 20 years, a variety of clinical symptoms appeared in the residents of this district (7). The treatment of these neglected symptoms should be undertaken vigorously.

For the treatment of inorganic and organic mercury poisoning, excretion of the mercury is indicated in the early stage. Attempts have already been made to accomplish this by the use of chelation drugs such as BAL, D-penicillamine, thiol resin, EDTA and tiopronin (2, 3, 9–17). These drugs are not considered effective for the treatment of the chronic stage of mercury poisoning or chronic Minamata disease, although they may be effective in promoting the excretion of mercury in a limited, early stage of the disease. Consequently, these drugs have not been used in the Minamata district for treating the disease during the past ten years. Moreover, it was generally believed that the incidence of Minamata disease had been halted and that symptoms of the poisoning would not

progress after the pollution was stopped.

Recent clinical and epidemiological investigations, however, revealed the fact that the district has been polluted continuously. The symptoms attributed to methyl mercury poisoning have been getting worse, and completely new symptoms have appeared among residents of this polluted district (5–7). Thus, in this study we planned to test once again the mercury-excreting drugs in addition to allopathic treatment and rehabilitation (18, 19).

Subjects and Methods

All subjects examined in this study were suffering from chronic Minamata disease, which may be defined by the following characteristics. 1) The first symptom of the disease appeared since the 1960s, and the progress of the disease is slow. (the delayed type) 2) clinical symptoms are varied, and the relative severity of each differs from case to case ; thus, when one symptom or another dominates, the patient may be diagnosed as having another disorder. (atypical type) 3) Generally, in the chronic phase, mercury value in the patients' hair, blood and urine is lower, and its diagnostic value is low. These chronic patients have a history of contamination over a long period. The mercury value in fish they are eating now is 1/50 to 1/100 that reported twenty years ago. 4) In addition to neurological symptoms, disturbances of other organs occur (16).

Chronic Minamata disease exhibits, in addition to its particular progression, patterns different from those of the acute or subacute type. The latter attack the patient abruptly, and are generally severe. Typical symptoms such as sensory disturbance, ataxia, dysarthria, concentric constriction of the visual field, auditory disturbance and tremor frequently appear, and little difference is observed in the severity of the symptoms. The chronic

Table 1. Neurological symptoms of subjects

	Cases in which spironolactone is used	Cases in which tiopronin is used
Sensory disturbance	15	50
Incoordination	9	25
Ataxic gait	7	15
Adiadochokinesia	9	25
Finger-nose test	6	21
Knee-heel test	9	23
Clumsy of finger movement	9	25
Muscular weakness	11	42
Auditory disturbance	13	45
Constriction of the visual field	8	39
Dysarthria	5	17
Tremor	10	35
Crampus	13	35
Muscular atrophy	4	17
Faintings fits	7	17
Hyperreflexia	8	23
Total	15	50

type, on the other hand, may be diagnosed incorrectly unless sensory disturbance of the glove or stocking type and the constriction of the visual field are performed.

The reasons are as follows. Ataxia and dysarthria are mild in some cases, while muscular atrophy or pyramidal syndrome are predominant in other cases. Psychotic symptoms may be conspicuous, but spinal syndrome or hemiplegia occasionally stand out. Some patients show only sensory disturbance, but subjective symptoms may be found in their families if members show typical forms of the disease. Although these symptoms are characteristic of chronic Minamata disease, they are similar to those seen in typical acute or subacute Minamata disease also. (Table 1)

Subjects were not only examined for neurological, psychotic and subjective symptoms but also were given various biochemical tests prior to the administration of the drug. The examinations or tests were performed in the course of drug administration when necessary.

The drugs used were tiopronin and spironolactone. Fifty cases given tiopronin and 15 given spironolactone provided the data reported below. Tiopronin was administered orally at doses of 300–600 mg per day (600 mg as a general rule) ; spironolactone was given orally at doses of 50–70 mg per day. During the period of administration, many patients were given hypotensive drugs, sedatives, vitamins and hepatotonics concomitantly. Tiopronin was administered for 2 to 24 months and spironolactone for 30 to 60 days. There were no dietary restrictions during these periods. Subjects capable of becoming pregnant were excluded from the study. Drugs were used with the permission of the patient, to whom the actions of the drugs were explained beforehand. In 19 cases treated with tiopronin and 15 with spironolactone, mercury levels in the blood and urine were regularly measured before and during the period of drug administration. The total mercury content was assayed by means of atomic absorption spectrophotometry (8).

Case Histories

Case 1 : 52 years, male, fisherman

Subjective symptoms, such as numbness and pains in the limbs, weakness of lower half of the body, impaired hearing and speech, stumbling, tremor, muscle twitch, cramps of lower limbs and fainting, have been getting worse gradually since around 1965. In 1975, sensory disturbance of the glove and stocking type at the extremities, constriction of the visual field, auditory disturbance, muscular weakness, muscular atrophy and tremor were confirmed. Concurrently, hypertension, liver disorder and diabetes were observed. The case was diagnosed as nearly-typical, chronic Minamata disease. Tiopronin was given at 600 mg/day together with a hypotensive drug. Mercury levels before administration were 4.35 ppm in the hair, 51 ppb in the blood and 3.5 μg/l (mean value) in the urine ; thus, the values were already at low levels. Two days after the administration of tiopronin, the excretion of mercury into the urine was 14.1 μg/l, and after 5 days it was 18.5 μg/l, indicating marked enhancement of excretion by the drug. The blood level of mercury, however, was not increased (Fig. 1). The treatment with tiopronin was continued for a period of 4 months. Neurologically, the numbness and tremor were found to be less noticeable, but no marked improvement could be observed. The patient described his

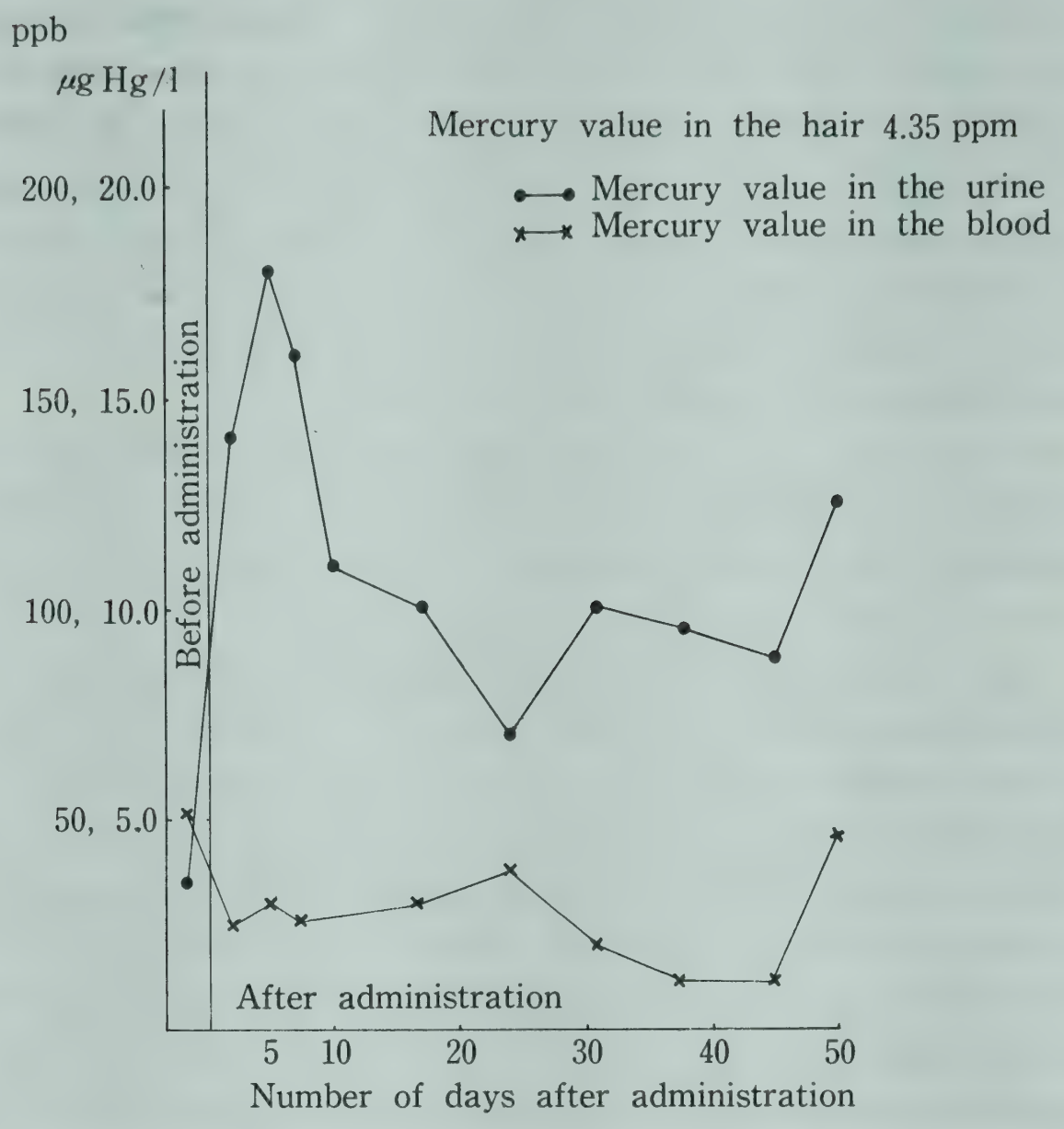

Fig. 1. Changes in mercury value of blood and urine associated with administration of tiopronin in Case 1.

subjective feeling by saying, "My body feels lighter than before." Neither side effect nor abnormality in hematochemical tests was observed.

Case 2 : 45 years, female, fisherman's wife

Her husband and parents, engaged in fishing, were suffering from acute and typical Minamata disease. Eight pregnancies had resulted in four miscarriages and three stillbirths. Since 5 or 6 years ago, the patient's limbs had felt numb with a kind of tingling. Subjective symptoms such as headache, pain in the limbs, dullness, fatigue, sleeplessness and fainting were conspicuous. The glove and stocking type sensory disturbance, auditory impairment and weakness, though mild, were observed as neurological symptoms. The case was diagnosed as Minamata disease from the epidemiological point of view as well.

Tiopronin was given at 600 mg/day together with sedatives and tranquilizers. Mercury levels in the blood and urine before administration were 44.5 ppb and 2.3 μg/l respectively. No increase in urinary excretion of mercury was observed on the third day of administration, but the excretion began to increase after about 10 days, when it reached 18.9 μg/l, and continued increasing as long as the drug was administered. Three months after the commencement of the treatment, the extent of the sensory disorders was found to have diminished. The patient said that the treatment was effective for headache, dullness and numbness. No side effect was observed. (Fig. 2)

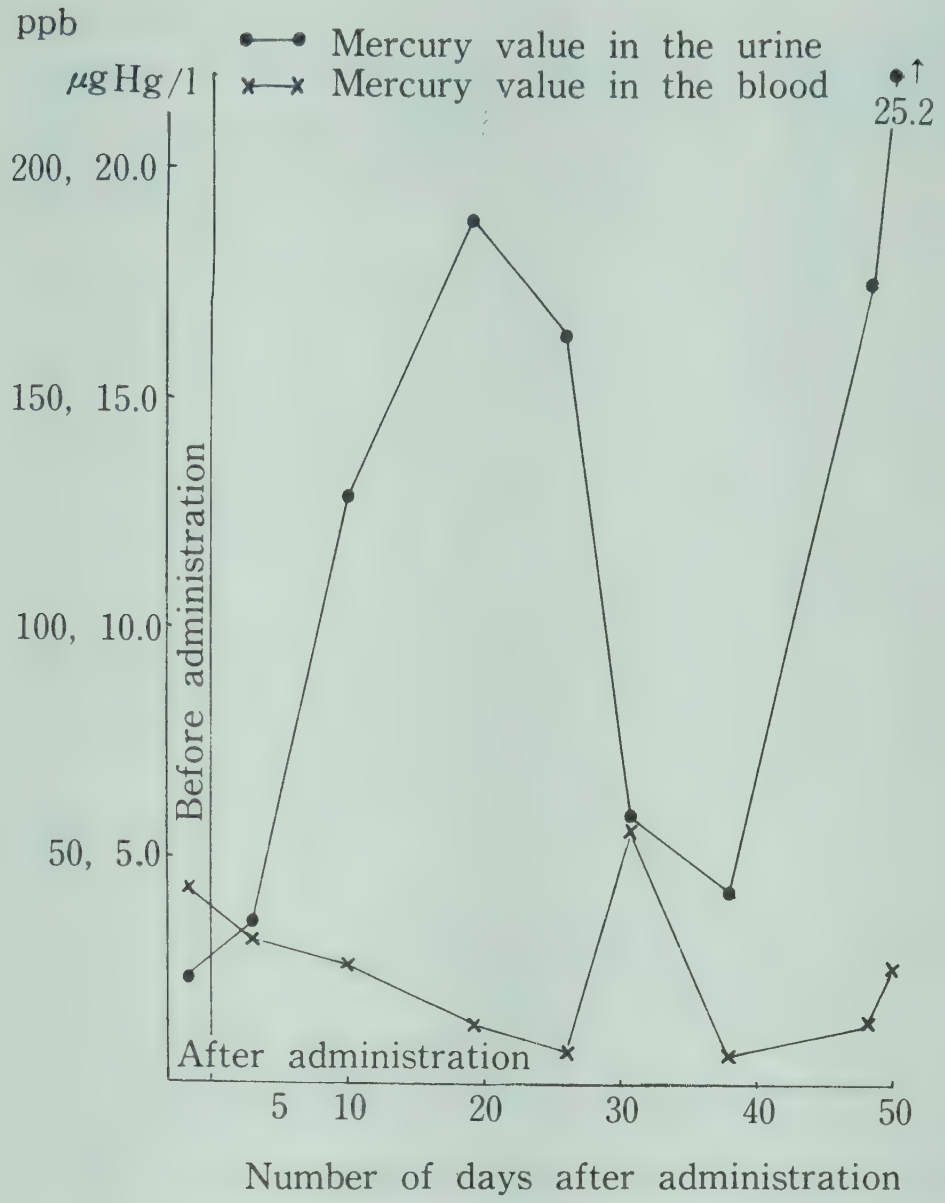

Fig. 2. Changes in mercury value of blood and urine associated with administration of tiopronin in Case 2.

Case 3 : 34 years, male, factory worker

His parents, engaged in fishing, suffered from typical Minamata disease. His elder sister was attacked by acute and severe Minamata disease in Octover 1954, at the age of 25, and died in July 1958. The autopsy confirmed the diagnosis of typical Minamata disease. The subject had been living with his family. In 1961, at the age of 22, he left home for six months to work as a laborer. He then experienced sensory disturbance of the hands, tremor due to fatigue, twitching, and cramps of the limbs. These first symptoms, however, did not affect his work seriously.

In August 1973, at the age of 34, the subject was seized by a nocturnal general convulsion. Thereafter, ataxia, auditory impairment and tremor appeared, resulting in temporary inability to sit up. After two or three days, however, spontaneous improvement allowed the subject to walk, and he recovered gradually. Clinical symptoms observed during hospitalization included numbness of the whole body, headache, dullness, forgetfulness, irritability and sleeplessness. The pupils were regular circles, the light reflex was normal, but eyeball movements were slightly unsmooth. Tongue movements were not smooth. Auditory disturbance, dysarthria, concentric constriction of the visual field, hypotonia, muscular weakness (notable over the left half of the body), hypoesthesia around the mouth and at distal end of the limbs (glove and stocking type), ataxic gait, incoordination in finger-nose, finger-finger, knee-heel test, adiadochokinesia, clumsiness of finger movements, and intention tremor were observed. Disorders in writing, thinking and

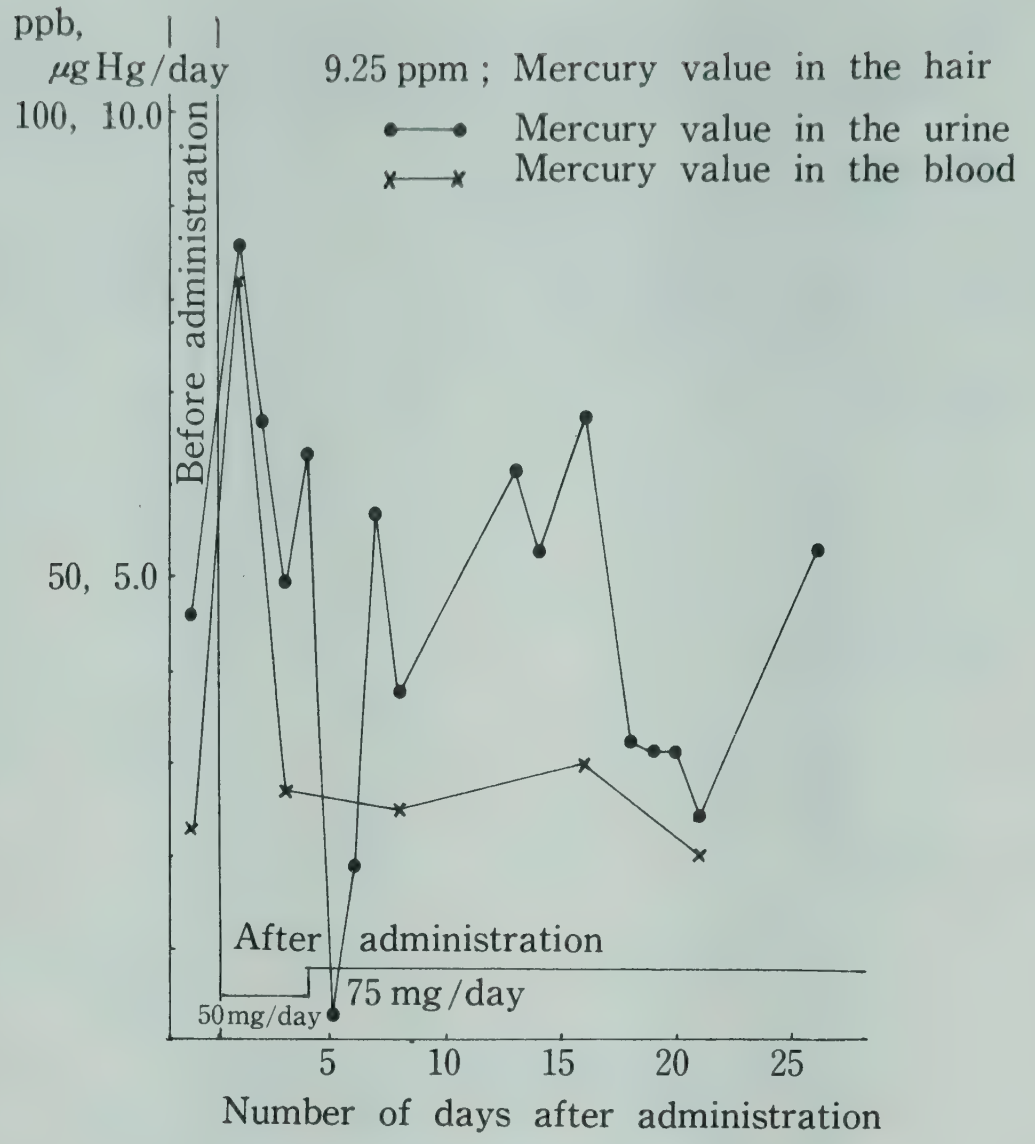

Fig. 3. Changes in mercury value of blood and urine associated with administration of spironolactone in Case 3.

calculation, and mental symptoms such as irritability, depression, nervousness and anxiety, were also observed. No causes other than brain disorder were detectable by various detailed tests. Minamata disease was suspected on the basis of epidemiological conditions, family history and life history. Levels of mercury, measured at the above-described stage, were 9.25 ppm in the hair, 22.5 ppb in the blood and 4.563 μg/day in the urine. These values suggested that the patient had not ingested much mercury recently.

Spironolactone was given at 50 mg/day for the first three days, then at 75 mg from the fourth day. Mercury content in the blood and urine increased to 82.5 ppb and 8.56 μg/day respectively at 24 hours after commencement of the drug administration. The blood mercury level remained approximately the same after 24 hours, the urinary mercury level increased, but with considerable variation (Fig. 3) (19). The volume of urine discharged during the treatment was within a range of 1,300-1,500 cc/day except for the first and the fourth days, when more than 2,000 cc was excreted daily. During the treatment, walking was stabilized and tremors were lessened. Moreover, pain in the limbs, painful localized cramps and general convulsive seizure disappeared, and mental stability was achieved. No side effect due to spironolactone could be detected. There was little change in the hematochemical findings. (Tab. 2)

Case 4 : 51 years, female, former fish dealer

The patient had been a fish dealer from 1956 to 1969, and had eaten large amounts of fish over a prolonged period. In 1962, when she was 39 years of age, numbness and

Table 2. Results of clinical-chemical test, Case 3.

	Before spironolactone was administered	During administration
Blood erythrocyte	434×10^4	488×10^4
Hb	90%	98%
leucocyte	4800	5500
Others	normal	normal
Urine Protein	−	−
Sugar	−	−
Urobilinogen	+	+
GPT	25 u	28 u
GOT	13 u	15 u
Thymol turbidity test	1.8 u	1.5 u
Zinc sulfate test	6.8 u	7.0 u
Serum protein	7.7 mg/dl	7.9 mg/dl
Albumin	64%	−
α_1 globlin	2.0%	−
α_2 globlin	9.4%	−
β globlin	10.8%	−
γ globlin	13.8%	−
Direct bilirubin	0.1	0.1
Alkalic phosphatase	7.1 u	7.3 u
Serum cholesterol	259 mg/dl	253 mg/dl
LDH	94 u	96 u
LAP	162 u	168 u
CPK	15 u	16 u
Serum amylase	80	91
Serum sugar	80 mg/dl	86 mg/dl
Blood urea nitrogen	11 mg/dl	13 mg/dl
Serum uric acid	5.8 mg/dl	5.5 mg/dl
Serum creatinin	1.5 mg/dl	1.5 mg/dl
Total lipoprotein	644 mg/dl	702 mg/dl
β-lipoprotein	160 mg/dl	162 mg/dl
Free fatty acid	0.61 mEq/l	0.70 mEq/l
Cholinesterase	1.0 u	0.8 u
Serum Na	142 mEq/l	135 mEq/l
K	4.4 mEq/l	11.9 mEq/l
Cl	102 mEq/l	99 mEq/l
Ca	4.4 mEq/l	4.2 mEq/l

*Note : The same test as that used in Case was conducted for each another case.

pain in the limbs appeared for the first time. The numbness spread gradually from the perioral area and distal ends of the upper and lower limbs to other regions of the body, leading to weakness of the legs and ataxia. In 1969, the patient found difficulty in grasping objects, and tremor also appeared. A clinical survey performed in 1973 aroused suspicion that the patient had contracted Minamata disease. In 1976 the patient was hospitalized in the neuropsychiatry facility at Kumamoto University. Sensory disturbance of glove and stocking type, auditory disturbance, ataxia, mild dysarthria, muscular weakness,

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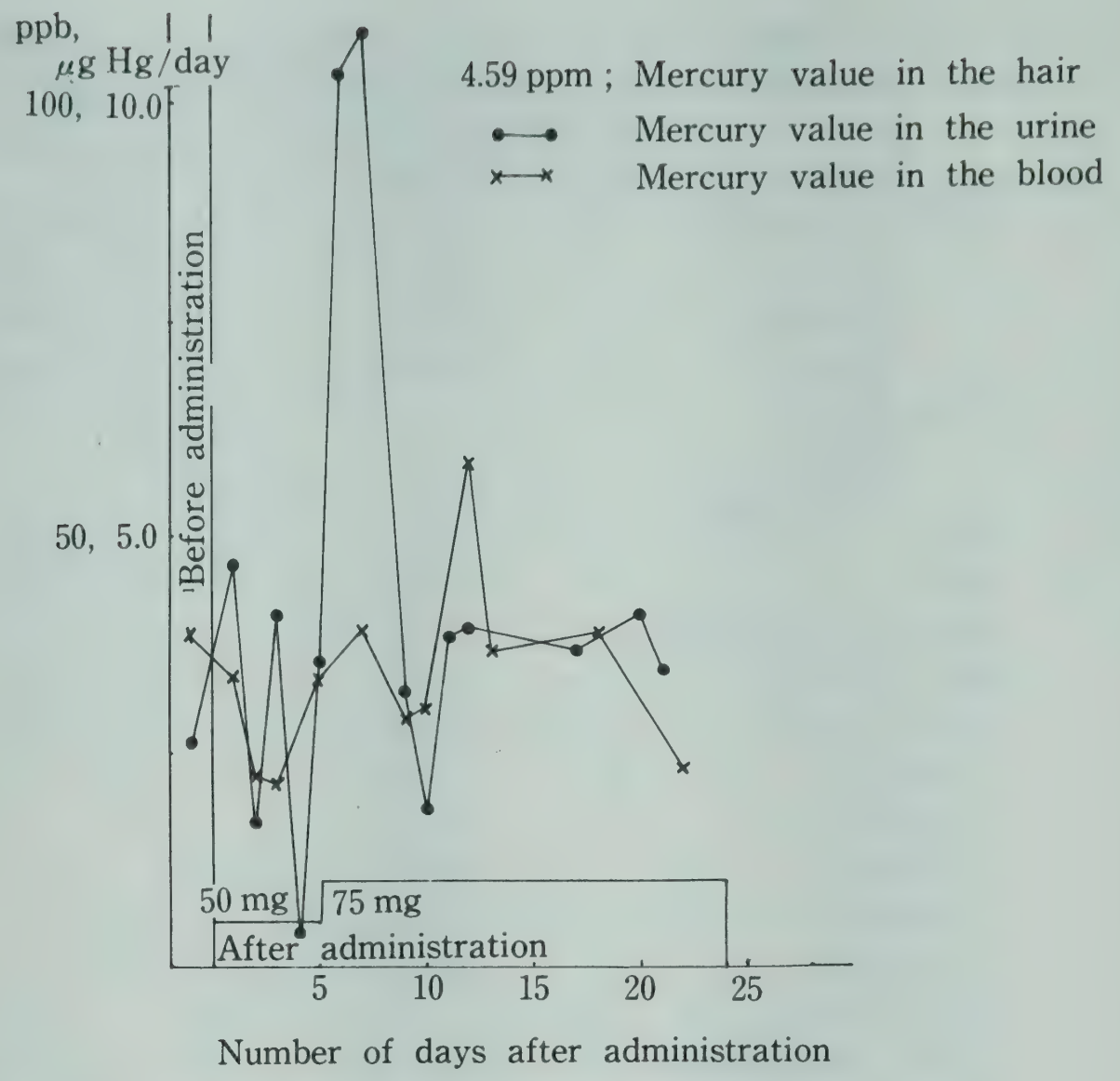


Fig. 4. Changes in mercury value of blood and urine associated with administration of spironolactone in Case 4.

concentric constriction of the visual field and tremor were noted on hospitalization. Increasing difficulty in walking was noted especially. No abnormality in the spinal cord was observed. Other detailed examinations showed a positive reaction to the glucose tolerance test and the presence of fluctuating hypertension. No other diseases which could have caused the symptoms under discussion were found.

Mercury levels at the time of hospitalization were 4.59 ppm in the hair, 39.5 ppb in the blood and 2.655 μg/day in the urine. The patient had stopped consuming large amounts of fish, but had been eating fish about once a week since 1969.

Administration of spironolactone increased the urinary mercury content to 4.72 μg/day. Although no change was observed in the blood mercury level, the urine content rose to a maximum of 10.368 μg/day when the dosage of spironolactone was raised to 75 mg/day (Fig. 4) (19). The volume of urine discharged increased from 1,500 cc/day to 2,000 cc/day during drug administration, resulting in the disappearance of edema from the lower limbs and stabilization of blood pressure. Both the neurological and subjective symptoms remained unimproved, however. No side effect or hematochemical change from the drug was detected.

Results

1) Mercury content in blood and urine of chronic Minamata disease patients

Mercury content of the blood in chronic Minamata disease patients was in the range

of 4–59 ppb (mean value=29.2 ppb), which is lower than that of patients with acute Minamata disease. The control mean value obtained from residents in Kumamoto city was 10 ppb, so the values found in the patients were appreciably higher than those of the controls.

Urinary mercury levels in patients with chronic Minamata disease was in the range of 0.4–9.2 μgHg/l, the mean value being 3.8 μgHg/l. These values were not significantly different from the control values obtained from 5 normal subjects. However, considerable individual differences and daily variations were observed to the urinary mercury level.

a) Effects of tiopronin

Transient increases of blood mercury content were observed sporadically in the 19 cases that allowed comparison of blood and urinary mercury levels before and after the administration of tiopronin. For instance, values such as 273 ppb and 106 ppb were recorded within one month after drug administration, and the value of 646 ppb also was obtained 4 months after administration, although this might be an exceptional case (Fig. 5). Generally speaking, however, a rapid and remarkable increase in the blood mercury level should not be expected from the administration of tiopronin. The urinary mercury level, on the other hand, was clearly raised by the drug. The maximum vallue of 38.4 μgHg/l was exhibited in one case, and mean values of the increases were two or three times the values prior to drug administration. Among these results, the maximum increase in value was nine times (Fig. 6). Individual differences and daily variations in the urinary mercury content, however, were still remarkably large.

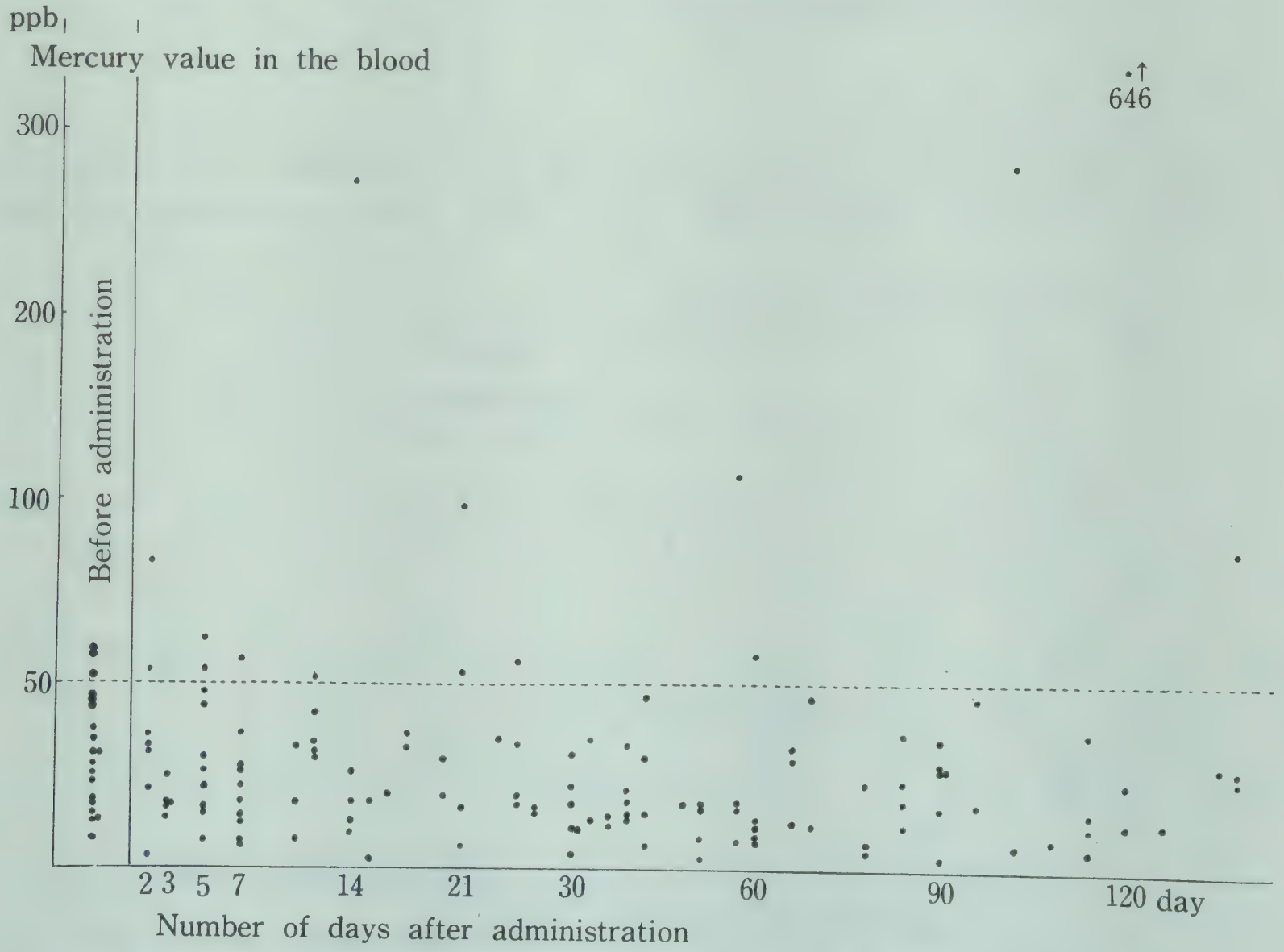


Fig. 5. Effect of tiopronin on mercury value of blood in chronic Minamata disease patients

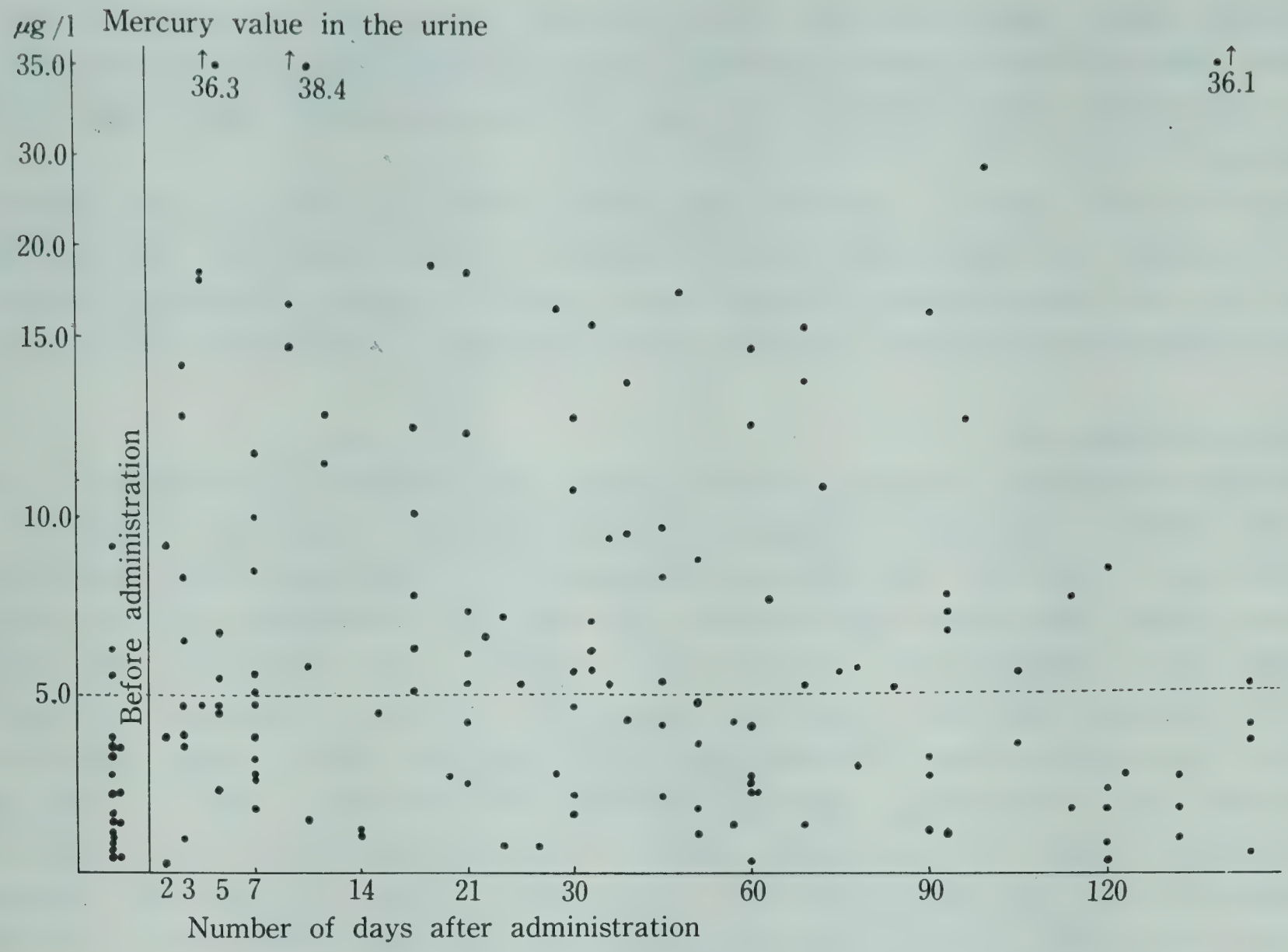


Fig. 6. Effect of tiopronin on mercury value in urine of chronic Minamata disease patients

b) Effects of spironolactone

Blood and urinary mercury content before the administration of spironolactone were compared with those after administration in 15 cases. One case showed the high value

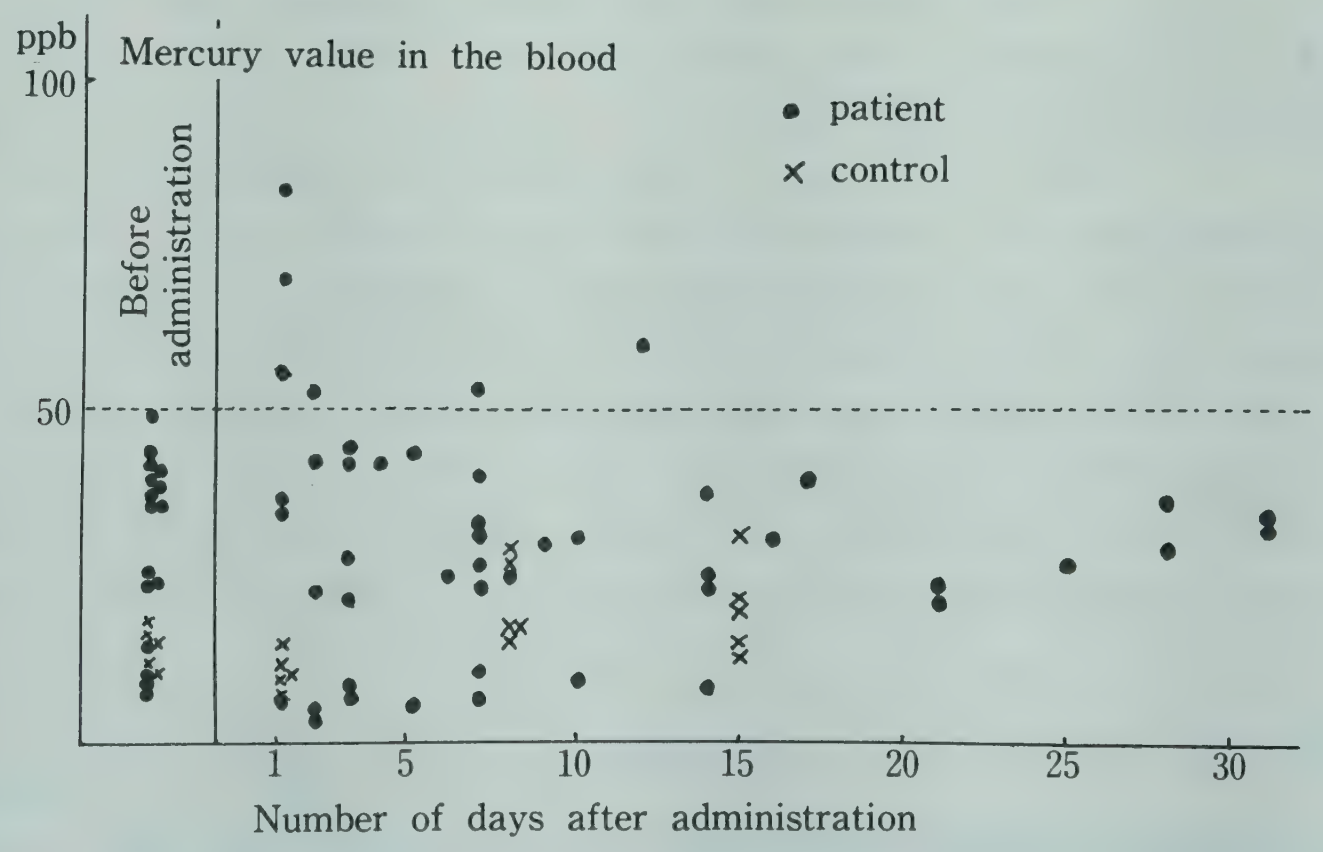


Fig. 7. Effect of spironolactone on mercury value in blood of chronic Minamata disease patients

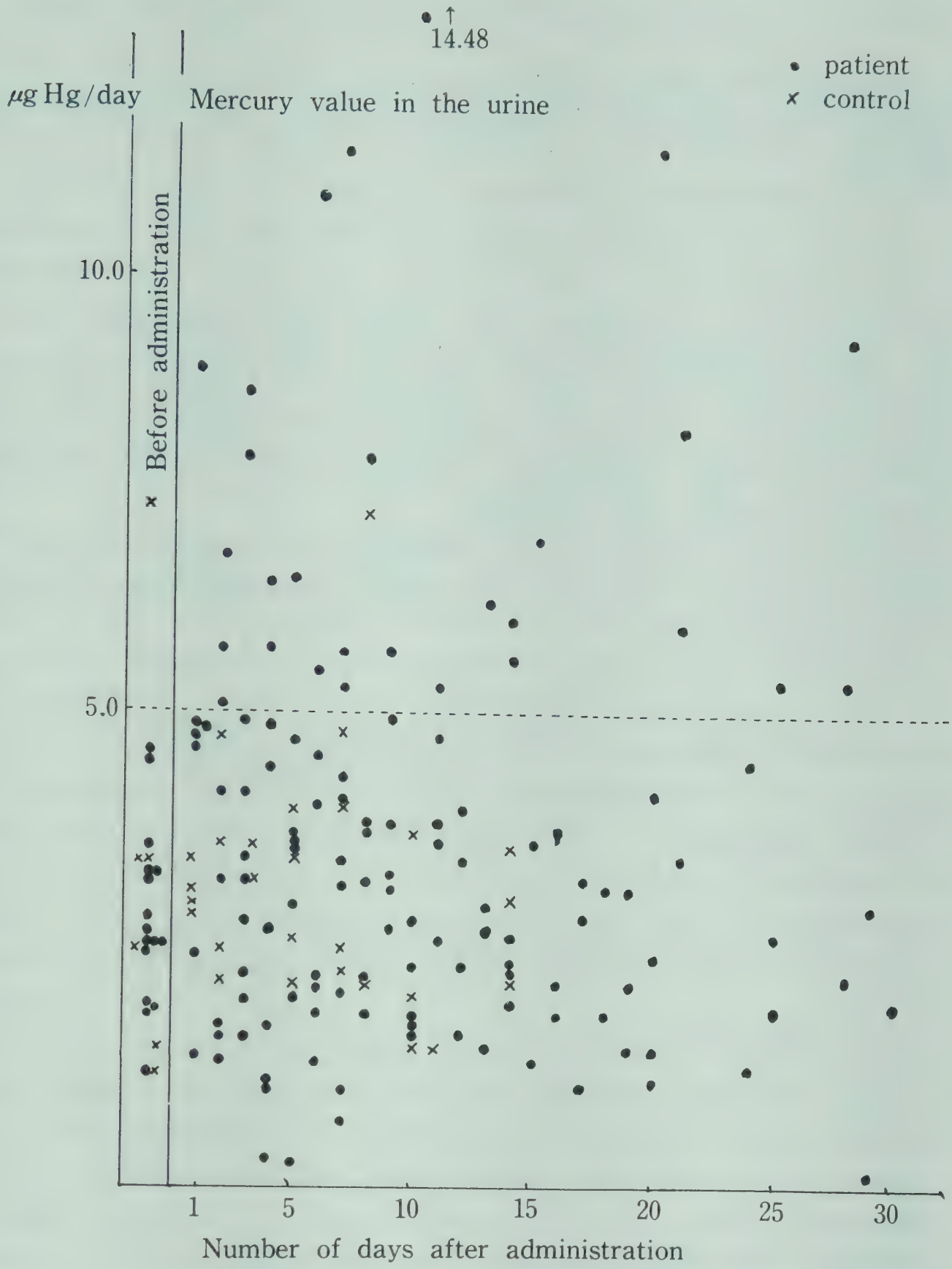


Fig. 8. Effect of spironolactone on mercury value in urine of chronic Minamata disease patients

of 82.5 ppb in the blood on the first day of treatment, and two cases gave values higher than 50 ppb (Figs. 3, 7). But on the whole, marked increases of value could not be obtained (Fig. 7).

Increases of the urinary mercury level were found in some cases (Fig. 8). However, only 28 cases (21.7 %) out of 129 cases showed values higher than 5.0 μg/day, and in general the increase was not remarkable. Even one week after administration of the drug, only 14 cases (23.3 %) out of 60 showed such a level of urinary excretion of mercury.

As no study of the effect of spironolactone on the urinary excretion of mercury had been made, five control cases were examined separately for this purpose. The results indicated that spironolactone might have some effect in promoting the urinary excretion of mercury in patients with chronic Minamata disease as compared with the control

subjects (Figs. 7, 8).

It is known that spironolactone has a diuretic action, and an attempt was made to correlate urinary volumes with amounts of mercury excreted. No reliable correlation could be obtained, however.

2) Clinical effects

The administration of tiopronin resulted in the relief of symptoms in 21 cases out of 50 cases examined. In 9 cases out of the 21, however, the symptoms recurred when the administration was interrupted. Subjective symptoms were alleviated by the drug. These included numbness (11 cases), headache (8 cases), cramps in the limbs (8 cases), fainting (6 cases), dullness, dizziness and insomnia.

In eight cases, symptoms were relieved by the administration of spironolactone. Cramps in the limbs were most responsive (7 cases), and headache, fainting, dullness, pain in the limbs etc were also improved (Tab. 3).

Table 3. Clinical effect

	Tiopronin	Spironolactone
Effective	9 } 21	3 } 8
Somewhat effective	12 }	5 }
No effective	27	7
Deteriorated	2	0
Numbness	11	2
Headache	8	3
Cramps in the limbs	8	7
Fainting	6	3
Dullness	6	3
Dizziness	5	2
Insomnia	5	0
Pain in the limbs	5	3
Clumsy in finger movement	4	3
Tremor	3	3
Weakness	2	3
Edema	0	3

Some neurological symptoms such as incoordination, sensory disturbance, muscular weakness and dysarthria resisted the drugs. Tiopronin relieved muscular weakness in 2 cases and tremor in 2 cases. Spironolactone altered several neurological symptoms in one patient (Case 3), and relieved tremor and clumsiness of finger movements in some other cases.

In approximately 50 % of the total cases examined, treatment was ineffective. Transient aggravation of numbness, without such aggravation of neurological symptoms, was observed in two cases treated with tiopronin. No consistent correlation between amounts of mercury excreted into the urine and clinical effects during treatment with the drugs could be obtained.

3) Side effects and results of clinical chemical tests

Of the patients treated with tiopronin, five showed side effects, namely ; two cases of a sinking feeling in the stomach ; three cases of stomachache ; two cases of nausea ; one case of tinnitus, and one case of wooziness accompanied by gastrointestinal upset. Administration of the drug had to be discontinued in the two out of these seven cases. As the administration of spironolactone increased the frequency of urination (pollakiuria), insomnia was observed in one case, and hypotension was occurred in another case.

Among the subjects suffering from chronic Minamata disease, many had prior complications. Among the fifty cases treated with tiopronin we found hypertension (18 cases), apoplexy (3 cases), diabetes (12 cases), liver disorder (13 cases), peptic ulcer (8 cases), anemia and cardiac disorder. Similar complications were noted in the cases treated with spironolactone (Tab. 4). Clinical examinations of these patients were conducted to determine the erythrocyte, leucocyte and blood platelet counts, levels of hemoglovin, Na^+, Ca^{++}, K^+ and Cl^- in the blood. Examinations or tests were made for serum protein, alubmin, globulins, total cholesterol, cholinesterases, free fatty acids, total lipids, triglycerides, alkaline phosphatase, LDH, blood sugar and its tolerance, urinary nitrogen, uric acid, creatine, creatinine, GOT, GPT, ZTT, TTT, and CPK. The triosorb test, rheumatic reactions and serum reactions for syphilis were performed. Also, urinary levels of proteins, sugar and urobilinogen were measured (see Tab. 2). In general, these examinations revealed no significant differences in the above clinical chemical values between patients with complications and those without. However, one case given tiopronin showed a rise in GOT and GPT values, and another given spironolactone showed the high blood K^+ level of 11.9 mEq/l.

Aggravation of a liver disorder was caused by the administration of tiopronin to a 40-year-old patient with typical chronic Minamata disease with a history of chronic hepatitis. The administration of 600 mg of tiopronin relieved dullness and pain in the limbs, but six months later the liver disorder was detected by clinical chemical tests and administration of the drug was interrupted at this stage. The patient asked to resume administration of the drug because of serious dullness. Therefore, administration of psychotropic drugs was stopped and tiopronin treatment was resumed. Levels of GOT and GPT were not stabilized and kept increasing, so the drug was stopped again after 8 months of treatment. The patient was then hospitalized and treated by rest, diet and

Table 4. Diseases, other than neurological symptoms, of subjects

	50 cases in which tiopronin is used	15 cases in which spironolactone is used
Hypertension	18	4
Appoplexy	3	0
Diabetes	12	2
Liver disorder	13	2
Anemia	5	0
Hypotension	2	0
Cardiac disorder	1	0
Cervical spondylosis	8	2

chemotherapy, which brought improvement. In this case, however, the concomitant use of many kinds of drugs and a history of chronic hepatitis must be considered, so the aggravation of the liver disorder should not be attributed solely to tiopronin.

4) Comparison of tiopronin and spironolactone

Tiopronin was more potent than spironolactone in increasing the urinary excretion of mercury. No marked increase was obtained by either drug in the blood mercury level.

Tiopronin brought improvement of subjective symptoms such as numbness, headache and dullness, while spironolactone was effective on cramps in the limbs. Both drugs were effective for neurological symptoms such as fainting, but the effect was observed in only a few cases. Approximately 50 % of the total cases were not affected by either drug.

Side effects due to tiopronin were gastrointestinal disorders. Those due to spironolactone were pollakiuria, insomnia and hypotension. No particular aggravation of complications by either drug was observed in the case accompanied by liver disorder, in which the rise of GOT and GPT levels was observed, or in the case in which spironolactone administration resulted in a high level of K^+ in the blood. These side effects were not considered serious, but it was necessary to take precautions.

Discussion

Tiopronin which were synthetized and developed by Santen Pharmaceutical Co. (Japan), is widely used for the prevention of secondary disorders due to treatment with carcinostatics (20, 21), *X*-ray treatment (22), therapy for Wilson's disease (23), gestational toxicosis (24), alcoholism and hemosiderosis (25, 26), and also for protection of the liver (25, 27, 28). Tiopronin, alternatively called N-(2-mercaptopropionyl)-glycine, is a synthetic compound of tiolactic acid with an SH radical and glycine (Fig. 9). As SH compounds have been known to be very effective for detoxication or promotion of metabolism, they are utilized for treatment of heavy-metal poisoning and other toxic conditions (10, 13–16, 29). In 1961 Sebe first reported that the administration of tiopronin could delay an attack of mercury poisoning and also enhance urinary excretion of mercury (30). The drug was thus suggested as appropriate for treating Minamata disease. In 1966, Tsubaki reported that tiopronin, administered in doses of 150 mg, 300 mg and 600 mg at a relatively early stage of Minamata disease, increased urinary excretion of mercury 3 to 6 times and also induced clinical improvements (17, 31). It has been reported also that poisoning with inorganic mercury can be relieved by tiopronin (11, 16).

Spironolactone, on the other hand, is a substance known to have an action antagonistic to adrenocortical aldosterone (Fig. 10). A steroid compound, spironolactone is believed to antagonize the action of aldosterone in the renal tubules, causing gradual and stable

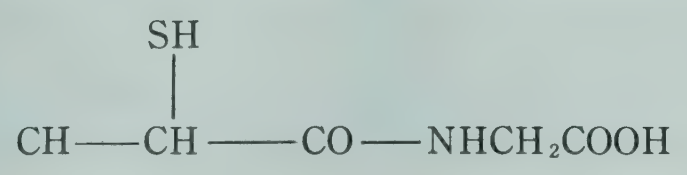
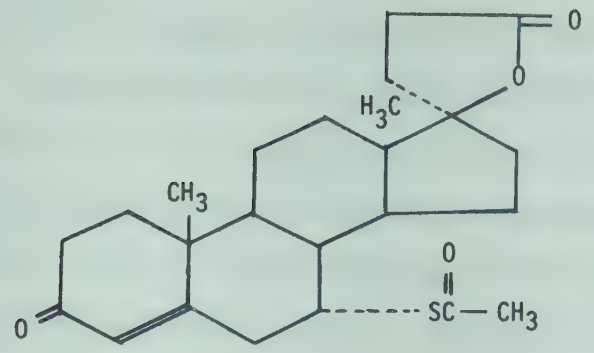


Fig. 9. *α*-Mercaptopropionyl-glycine (Tiopronin)



7α-acetylthio-]7-hydroxy-3-oxo-]7α-pregn-4-ene-21-carboxlic acid γ-lactone

$C_{24}H_{32}O_4S = 416.58$

Fig. 10. Spironolactone (Aldactone-A)

lowering of blood pressure without causing either loss of blood K^+ or affecting blood sugar and serum uric acid levels (32–35). Moreover, spironolactone is effective in preventing arrhythmia and ventricular extrasystole due to the administration of digitoxin (36, 37), in suppressing anesthetic action (38), and in preventing side effects or poisoning from various drugs (39–41).

The first report about the use of spironolactone in mercury poisoning was published by Selye in 1970 (42). He suggested that pre-treatment of the rat with spironolactone may prevent death due to acute mercury poisoning and renal cortical disorder. The results were confirmed later by Haddow (43, 44), Garg (45) and Abe (46), and similar effects of spironolactone in methyl mercury poisoning were also confirmed by Pekkenen (47) and Takahashi (48). It was shown by animal experiments that spironolactone may reduce the amount of mercury accumulated in blood and tissues, enhancing the action of the drug upon mercury excretion. This process plays an important role in the suppressive action of spironolactone on mercury poisoning. Since investigations have been carried out with laboratory animals only, the mechanism of the action of the drug on human beings is not clear.

In this study, two drugs having different chemical structures and activities, i. e., tiopronin and spironolactone, were tested in the treatment of chronic Minamata disease. Experience in treatment of acute or subacute mercury poisoning with tiopronin has been reported, and there is no doubt about the action of the drug in promoting urinary excretion of mercury (2, 17, 30, 31). Little was known, however, about the effect of the drug on chronic Minamata disease. Nothing had been reported about the use of spironolactone for mercury poisoning in man. As these two drugs have now been used for the treatment of various diseases and their clinical safety has been confirmed with some reservations (20–29, 32–39), the drugs were considered suitable for testing in the present study. Even so, the drugs would not have been given to patients with chronic Minamata disease except under the circumstances described below.

It has been almost 20 years since Minamata disease, discovered in 1956, was proved in 1959 to be due to methyl mercury poisoning (2, 6). We know that nerve tissue, once damaged cannot be easily restored. It has been believed, in general, that mercury chelating agents such as D-penicillamine are effective only in a very limited (12, 17), early period of Minamata disease, and that if nerve damage has occurred in such patients, it is probably too late to use the drugs beneficially. Therefore no attempt was made

during the past ten years to treat Mianamata disease with these drugs. Clinical-epidemiological investigations rèvealed that pollution with mercury has spread to wider area and is more serious than was believed previously (5–7). Pollution is still continuing, and symptoms of the poisoned patients are gradually progressing (6, 49). Also, a study conducted at Niigata University confirmed that termination of the intake of mercury does not stop the aggravation of symptoms, but that administration of tiopronin to the patients up to 10 years after onset still may triple or quadruple urinary excretion of mercury (31).

Natural excretion of methyl mercury from the body in Minamata disease is very slow, as demonstrated by Takeuchi *et al* in laboratory experiments with animals (2–4). Autopsies of chronic Minamata disease patients showed methyl mercury levels of 0.08–0.13 ppm in the brain, 0.12–0.78 ppm in the liver and 0.18–1.20 ppm in the kidney (50). These values were higher than those in the control subjects, which were 0.009 ppm in the brain, 0.07 ppm in the liver and 0.02 ppm in the kidney (50). On the basis of these findings, the aggravation or appearance of symptoms in chronic Minamata disease patients might be interpreted as the delayed action of methyl mercury accumulated in the body (5, 6, 49). Therefore, the present authors considered drugs capable of excreting mercury from the body. D-penicillamine and BAL, of course, belong to this group of drugs. But tiopronin and spironolactone were chosen for this study because of the relative absence of side effect and low cost. Tiopronin has been reported to be more effective than D-penicillamien on mercury excretion (31). This fact was another reason for the choice of this drug for testing.

Confirming previous reports, the mercury excreting action of tiopronin in Minamata disease was demonstrated (2, 17, 31). The excreting action was observed not only in subjects working in a district polluted with mercury, but also in healthy subjects, thus suggesting that the action is not specific to Minamata disease patients (11, 16, 26). However, Shirakawa reported that tiopronin-induced urinary excretion of mercury in patients whose hair content of mercury was higher than 200 ppm at the time of onset was different from the excretion of patients whose hair content of mercury was lower than 200 ppm (31). This was true even in patients who had suffered from the disease for more than ten years. Therefore, it may be that the part of the mercury excreted into the urine after administration of tiopronin is mercury accumulated in the body. Attempts were made to estimate the extent of contamination in the past and the degree of previous clinical symptoms from amounts of urinary excreted mercury, but no consistent correlation could be observed. Similar results were obtained by using spironolactone, though the mercury excretion effect of this drug was weaker than that of tiopronin.

Chronic Minamata disease patients in the Minamata district have been polluted continuously over a prolonged period (7). It is no wonder, then, that the levels of urinary mercury excreted at the present stage through the use of tiopronin and spironolactone are not correlated with clinical symptoms. In addition, these subjects continue to eat large amounts of fish. In general, levels of mercury in the fish are lower than the safety standard. However, pollution with mercury continues to some extent, and the intake of such a large amount of fish might result in the accumulation of more mercury in the body. Therefore, not all of the mercury excreted into the urine during the drug treatment may be that which has accumulated in the body, since the diet of patients

during drug therapy was unrestricted.

It has been pointed out in studies with BAL that if the administration of mercury-excreting agents causes the release of mercury and a transient rise in the mercury level in the blood, the mercury passes the blood-brain barrier according to its concentration gradient, thus aggravating the symptoms (10). Laboratory experiments with animals demonstrated no such reinvasion of the brain by mercury after the administration of tiopronin. However, an abrupt and transient increase of blood mercury level may not be desirable. As described in the "Results" section, tiopronin and spironolactone did not produce such an abrupt rise of the blood mercury level. A similar possibility may be considered for the blood-placenta barrier. Therefore, human subjects who are pregnant or could become pregnant should not be treated with these two drugs.

As far as chronic Minamata disease is concerned, tiopronin and spironolactone cannot be expected to have such effects as those seen in acute or subacute cases. It is noteworthy, however, that tiopronin was found useful for subjective symptoms such as numbness, pain, headache and edema, although ordinarily symptoms of the chronic Minamata disease are expected to be affected by drugs. Chronic Minamata disease patients have trouble in daily life due to these subjective symptoms, so even partial relief from suffering is worth noting. However, in the consideration of effects, spontaneous variations in symptoms of the chronic Minamata disease and the psychological effect of personal relations between therapist and patient should not be ignored.

In any case, the effect of the drug on chronic Minamata disease is not like that seen in a continuous state of strong pollution, as in acute or subacute Minamata disease. As reported recently, relatively new cases such as those in Iraq (9) and Canada (51) might still be improved by the drugs. An important point in chronic Minamata disease is its gradual progress. Thus, it is reasonable to expect that administration of the drug for a certain period during this gradually progressing stage may arrest the disease. It will be interesting to see whether there is any clinical difference, after five or ten years from the onset of the disease, between cases treated with mercury excreting drugs and those not so treated.

It is obvious that neurological symptoms are characteristic of Minamata disease. The authors are inclined to believe that in the case of chronic Minamata disease there are various effects of methyl mercury upon other organs as well (6). In the past, these influences have been treated as accidental complications. The authors suspect, however, that methyl mercury might be connected with liver, kidney and cerebral vascular disorders as well as diabetes observed in chronic Minamata disease patients. Although the correlation between methyl mercury and these disorders has not been clarified, from the viewpoint of side effects the possibility of its influence on organs other than the nervous system in the treatment of chronic Minamata disease should not be ignored. As tiopronin and spironolactone were originally used widely in treating liver disorders, these drugs are theoretically superior to other chelating agents utilized only for excreting mercury. With the exception of gastro-intestinal disorders due to tiopronin and hypotension due to spironolactone, no serious side effects from the drugs were observed. Minute side effects have been reported, but the use of the drugs, even in cases with complications, was seemed acceptable in this study on the condition that due caution be observed. The

aggravation of liver function disorders by tiopronin, observed in the present study, cannot be attributed to tiopronin only. However, there is no doubt about the necessity of paying particular attention to the treatment of patients with hepatic disorders, not only on the basis of this study but also in view of previous reports that allergic liver disorders may be caused by tiopronin (52). Moreover, preventive use of the drugs in large dosages, solely because contamination has occured, should be avoided.

Summary

1. The treatment of chronic Minamata disease patients with tiopronin and spironolactone was undertaken. Fifty patients were treated with tiopronin, and 15 patients with spironolactone.
2. Administration of tiopronin at doses of 300–600 mg/day increased urinary excretion of mercury by 2 to 9 times despite a lapse of more than ten years since the onset of the disease. Spironolactone administered at doses of 50–75 mg/day also increased urinary mercury excretion, but its potency was less than that of tiopronin. The blood mercury level rose in two or three cases, but the increases were not remarkable.
3. In 21 out of 50 cases, tiopronin was judged as effective. Spironolactone was effective in 8 out of the 15 cases treated. Tiopronin was effective on subjective symptoms such as numbness (11 cases), headache (8 cases), cramps of the limbs (8 cases), fainting (6 cases), dullness (6 cases), dizziness, and insomnia. With spironolactone, improvement was observed in 7 cases of cramps in the limbs, 3 cases of headache, 3 cases of fainting, 3 cases of edema, and 3 cases of pains in the limbs. In one case, neurological symptoms were relieved.
4. Tiopronin administration caused side effects in 7 cases, namely a feeling of gastric fullness in 4 cases, stomachache in 3 cases, nausea in 2 cases and tinnitus in one case. Pollakiuria, insomnia and hypotension (one case each) from administration of spironolactone were observed. The rise of GOT and GPT values occurred in one case treated with tiopronin, and the increase of blood K^+ level in another case treated with spironolactone, suggesting the need for taking precautions in these respects during drug administration.
5. The clinical action of drugs with mercury excreting potency was not remarkable in cases of chronic Minamata disease. However, chronic aggravation of symptoms by mercury remaining in the brain is occurring at the present stage of the disease. Therefore, the use of these drugs is considered to be beneficial, but observation of the progress of patients under the drug treatment must be continued over a much longer period of time before definite conclusions can be reached. Moreover, treatment of organs other than nervous system should also be included in the management of chronic Minamata disease. (Author's abstruct)

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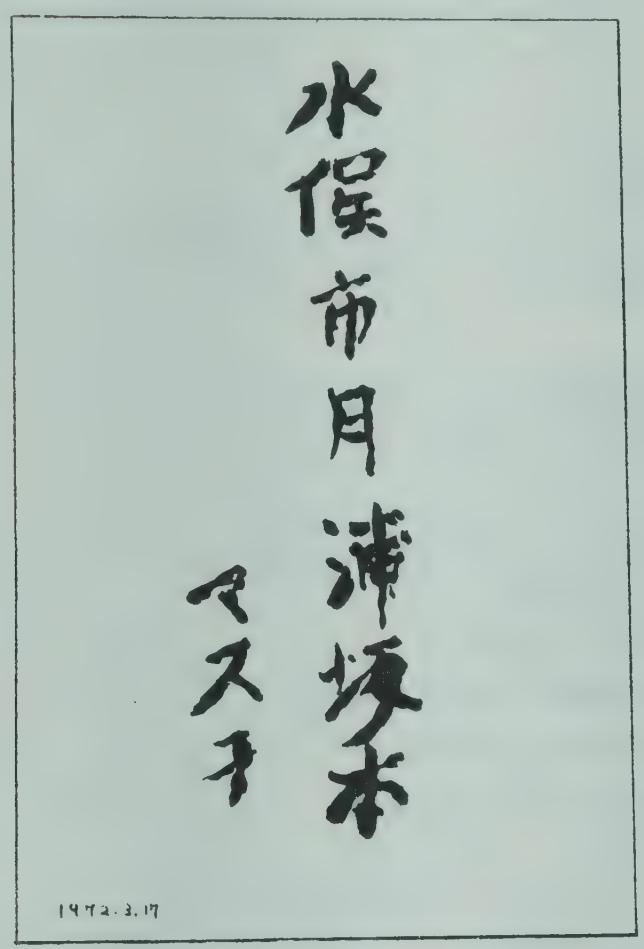

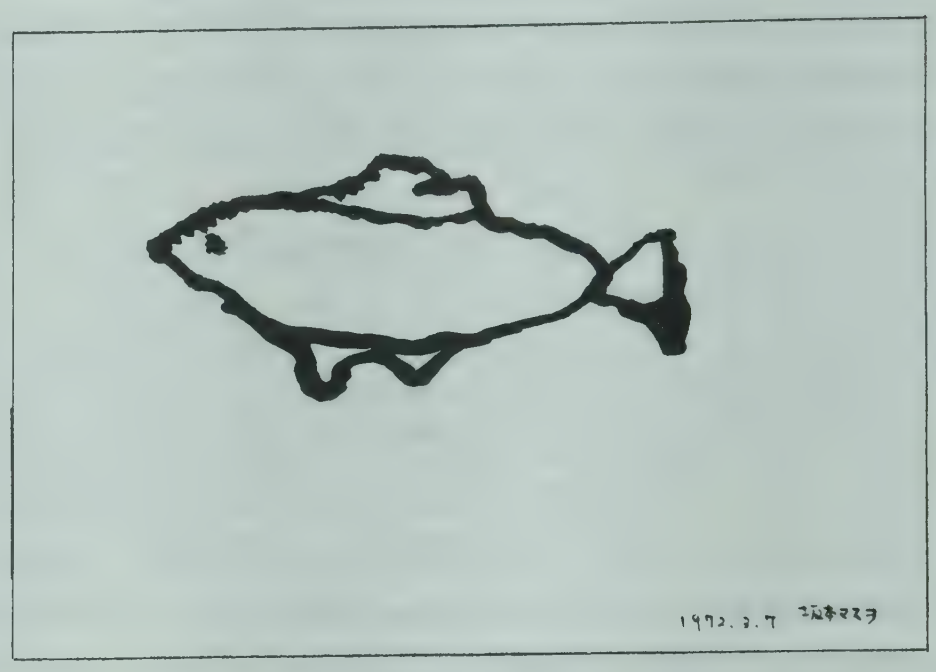

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MERCURY CONTAMINATION IN HUMAN HAIR AT INDIAN RESERVES IN CANADA

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Summary. In March and August 1975, a health survey of 89 inhabitants, of whom 71 were examined on mercury content in the hair, was conducted in the province of Ontario, Canada. The highest mercury content in the hair was 80.3 ppm and, among these 71 subjects, 44 showed more than 20 ppm and 23 more than 30 ppm. Mercury values in the hair were positively correlated with the quantity of fish in the diet, and higher in summer when fishes were eaten in larger quantities. These facts lead to the conclusion that mercury contamination of the body is caused by ingesting fishes caught locally.

The authors' limited survey did not reveal typical cases of Minamata disease among the Canadian inhabitants. However, there were 15 cases of glove and stocking type sensory disturbance, and 9 cases of paraconcentric constriction of the visual field. The cases with neurological symptoms showed higher mercury values in the hair than those without the symptoms, and were suspected of mild methylmercury poisoning.

Introduction

In 1970, in the district surrounding the water system of Wabigoon and English rivers in Ontario, Canada, fishes highly contaminated with mercury were discovered (1) (Fig. 1). Later a high content of mercury was also found in fishes and birds of this area and in the mud at the bottom of Clay Lake (2–8). The source of pollution was a chemical plant at Dryden, situated upstream (6). The cat ingesting fishes caught in this water system contracted methylmercury poisoning (9), which could be induced experimentally by feeding the animal with the mercury-contaminated fish (4, 10). In Minamata and Niigata, methylmercury poisoning in cats was observed concurrently with Minamata disease among inhabitants therein (11–15).

Since, in 1970, the above-mentioned circumstances indicated a very dangerous situation, the Provincial Government of Canada prohibited commercial fishing in the area, and examined mercury in the blood as well as in the hair of the inhabitants (9, 16). Actually to determine the mercury pollution, the authors visited the locality in March and August 1975 and conducted epidemiological and clinical surveys as well as analysis of mercury content in the hair. The present communication describes relationships

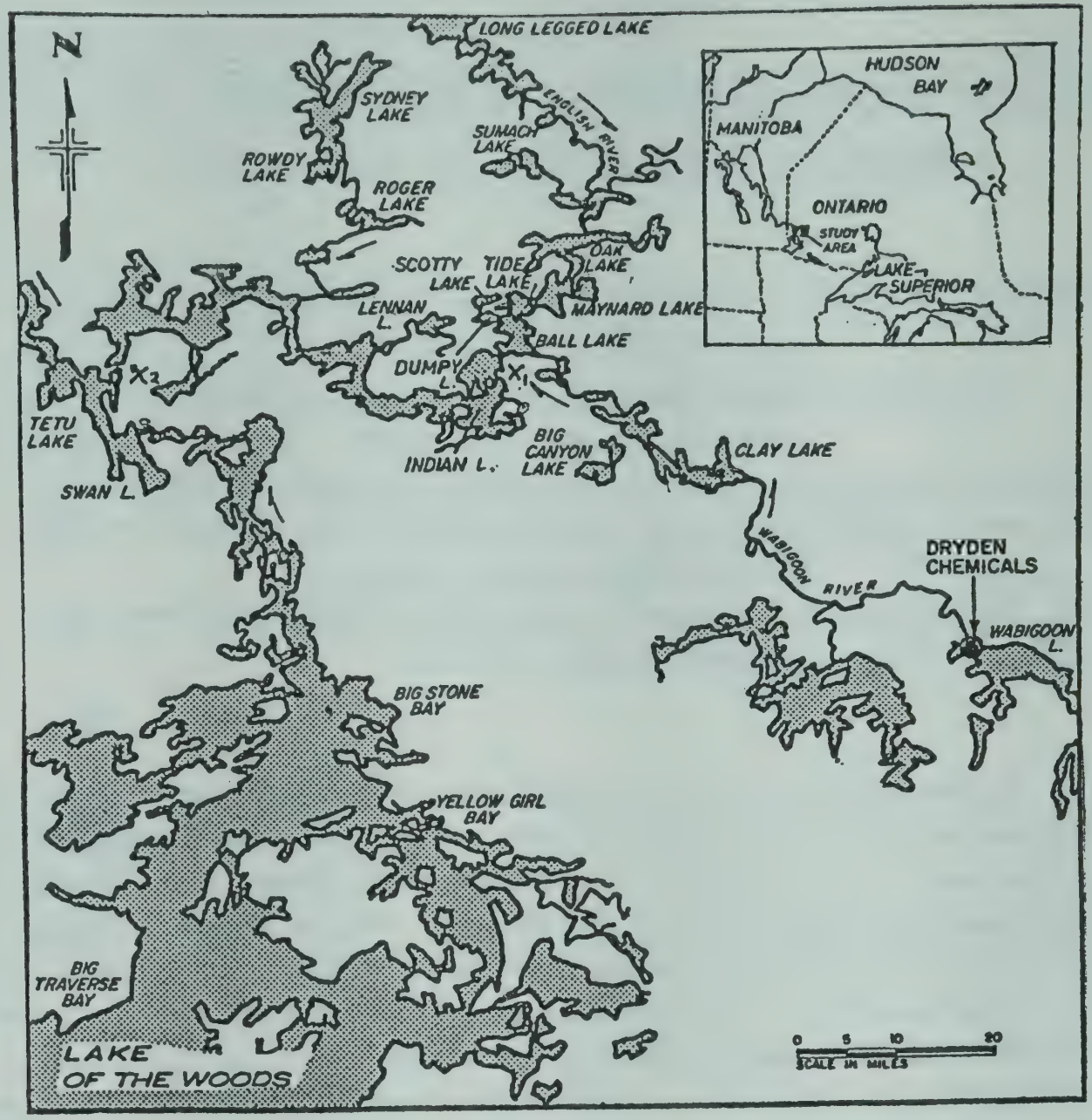

Fig. 1. Sketch map of Wabigoon river system

From Fimreite, N. and Reynolds, L. M.: *J. Wildlife Management*, **37** (1973), 63

X_1: Grassy Narrows, X_2: White Dog.

between mercury contents in the hair and neurological symptoms among the inhabitants.

Methods and Subjects

The health survey on 89 inhabitants of two reserves was conducted by the same methods as applied to the mass examination on Minamata disease in Japan (17,18). The clinical study consisted of routine neurological examination and examination of the visual fields using Förster's perimeter. The subjects for survey were fishing guides, fishermen and their family members. Hair samples of 71 inhabitants were also subjected to measurement of mercury content. The hair sumple was cut as close to the scalp as possible. The sample was cut at 3-cm intervals from the root (the scalp), and mercury content in each section determined by the Cold Vapor Method of atomic absorption spectrophotometry (19); estimating growth of the hair to be 1-cm a month, the degree of mercury pollution can be calculated roughly over three-month period.

Results

Some inhabitants in the regions still showed high mercury values in the hair, in-

dicating a persistent contamination with mercury; for instance, the most proximal segment (the first 3 cm from the scalp) of a hair sample representing the most recent contamination showed a highest value 80.3 ppm. Out of 71 inhabitants, 44 showed more than 20 ppm in the hair and 23 more than 30 ppm.

As shown in Figs. 2–A and 2–B, the mercury level of the hair indicated considerable variations from one subject to another and, moreover, marked fluctuations, even in an individual, from one segment to another. A comparison of mercury levels in the hair between the groups, the one with a dietary habit of continuously ingesting fish (caught in the polluted water system) and the other without such a dietary habit, disclosed a remarkable contrast (Fig. 2–A, 2–B) indicating that the difference in mercury levels was associated with consumption of fishes caught in the polluted river system. Furthermore, the segmental analysis of hair pointed out that the segments corresponding to growth of the hair from March through August had much higher mercury levels than those from September through February. The seasonal fluctuations appeared to

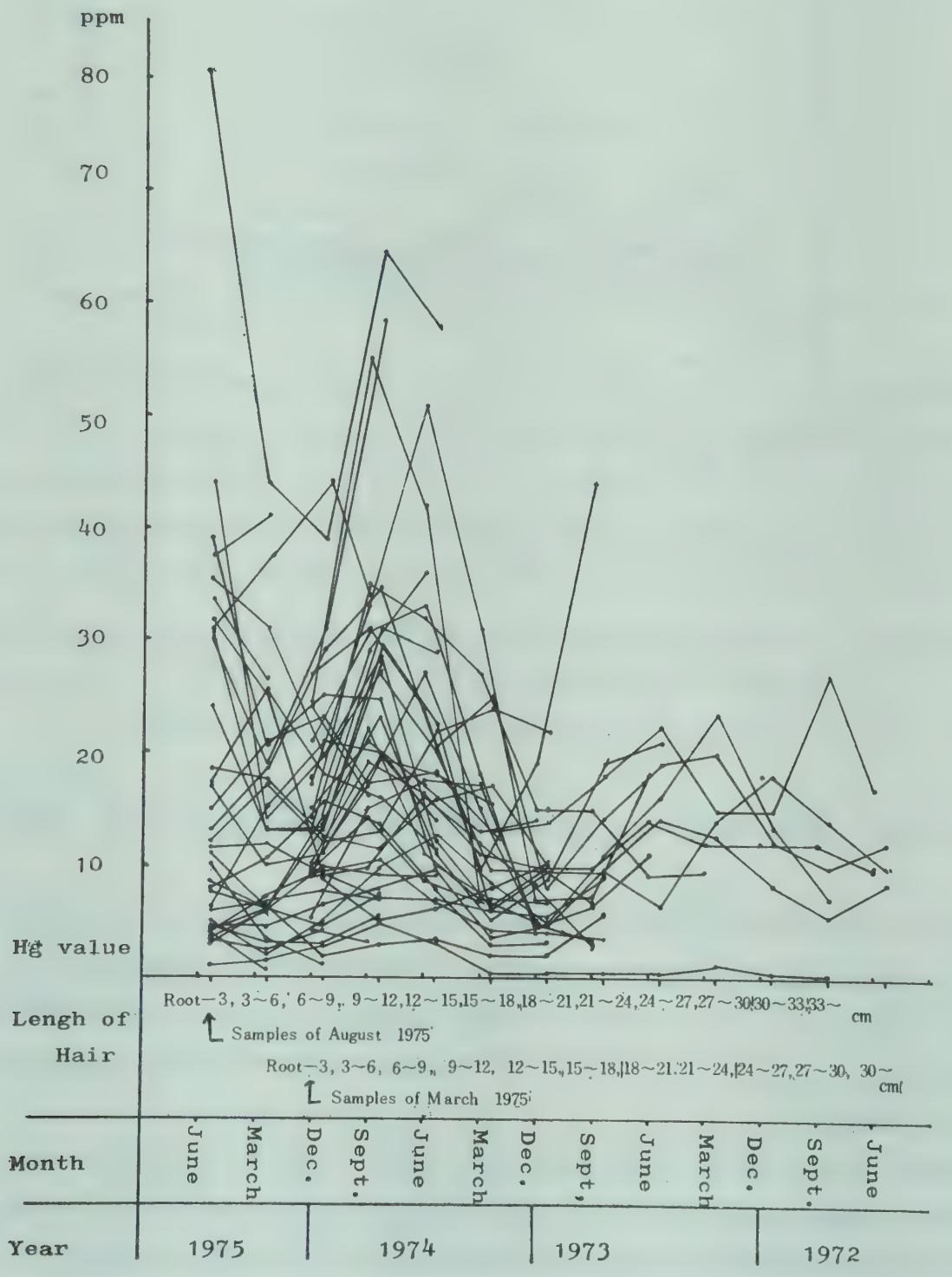

Fig. 2–A. Correlation between intermittent mercury concentration in the hair and ingestion of fish

Group that replied "do eat fish during summer"

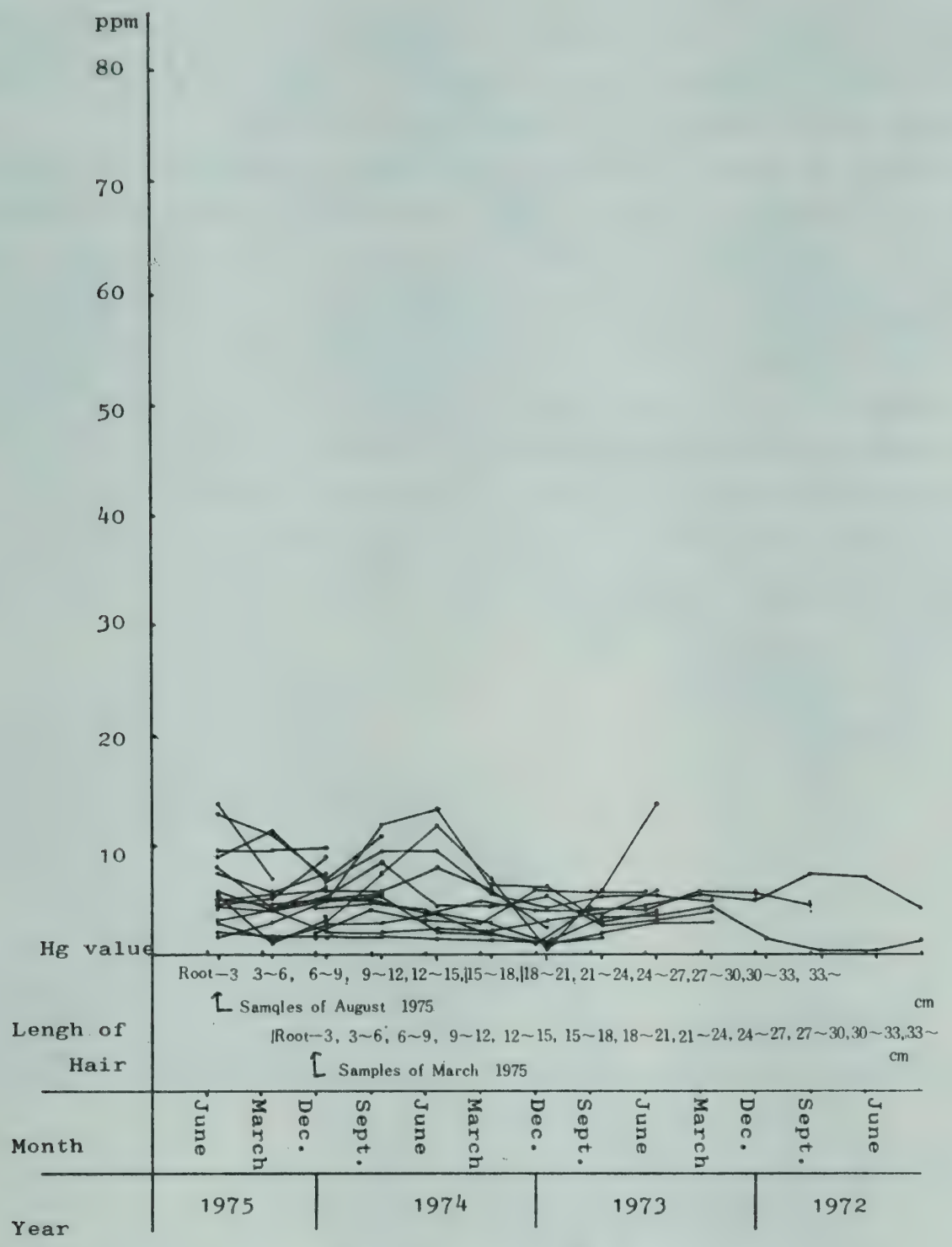

Fig. 2–B. Correlation between intermittent mercury concentration in the hair and ingestion of fish

Group that replied "not eating fish since 1970"

be parallel with fish consumption, which was obviously greater in amount during the hot season.

A neurological evaluation of the cases with a "high" level of mercury in the hair did not disclose signs and symptoms typical (complete) of Minamata disease, such as concentric constriction of the visual field, ataxia, sensory disturbance, disarthria, auditory disturbance, tremor *etc.*; however, various neurological symptoms were found in the habitants (Table 1).

The combination of fairly characteristic signs (paraconcentric constriction of the visual field, 9 cases; glove and stocking type sensory disturbance, 15 cases) with familial occurrence of the neurological manifestations and with high mercury levels in the hair strongly suggested that neurological symptoms had been caused by methylmercury. Some relationship between clinical symptoms and mercury contents in the hair may also be found, as shown in Fig. 3.

In the following groups with objective symptoms (A, B, C), mercury values in

TABLE 1. *Clinical symptoms (89 cases)*

		Number of cases
Subjective symptoms (complaints)	Numbness	28
	Pain in limbs	40
	Convulsion of limbs (Cramps)	16
Neurological symptoms	Disturbance of eye movement	19
	Nystagmus	3
	Impaired hearing	40
	Sensory disturbance	37
	(glove and stocking type)	(15)
	(perioral area)	(5)
	Abnormalities in the visual field	16
	(para-concentric contraction)	(9)
	Tremor	21
	Hyporeflexia	20
	Hyperreflexia	15
	Muscular weakness	16
	Ataxia	8
	(when walking on straight line)	(8)
	(adiadokokinesis)	(16)
	(dysmetry)	(7)
	Dysarthria	5
	Fainting-fit	2

the hair were higher than those for inhabitants with only subjective symptoms (D) or none at all (E); these groups include A) patients with abnormality of the visual fields (inclusive of concentric constriction) as well as sensory disturbance, B) those with other neurological symptoms such as auditory impairment as well as sensory disturbance, and C) those without sensory disturbance but with neurological disturbance (Fig. 3).

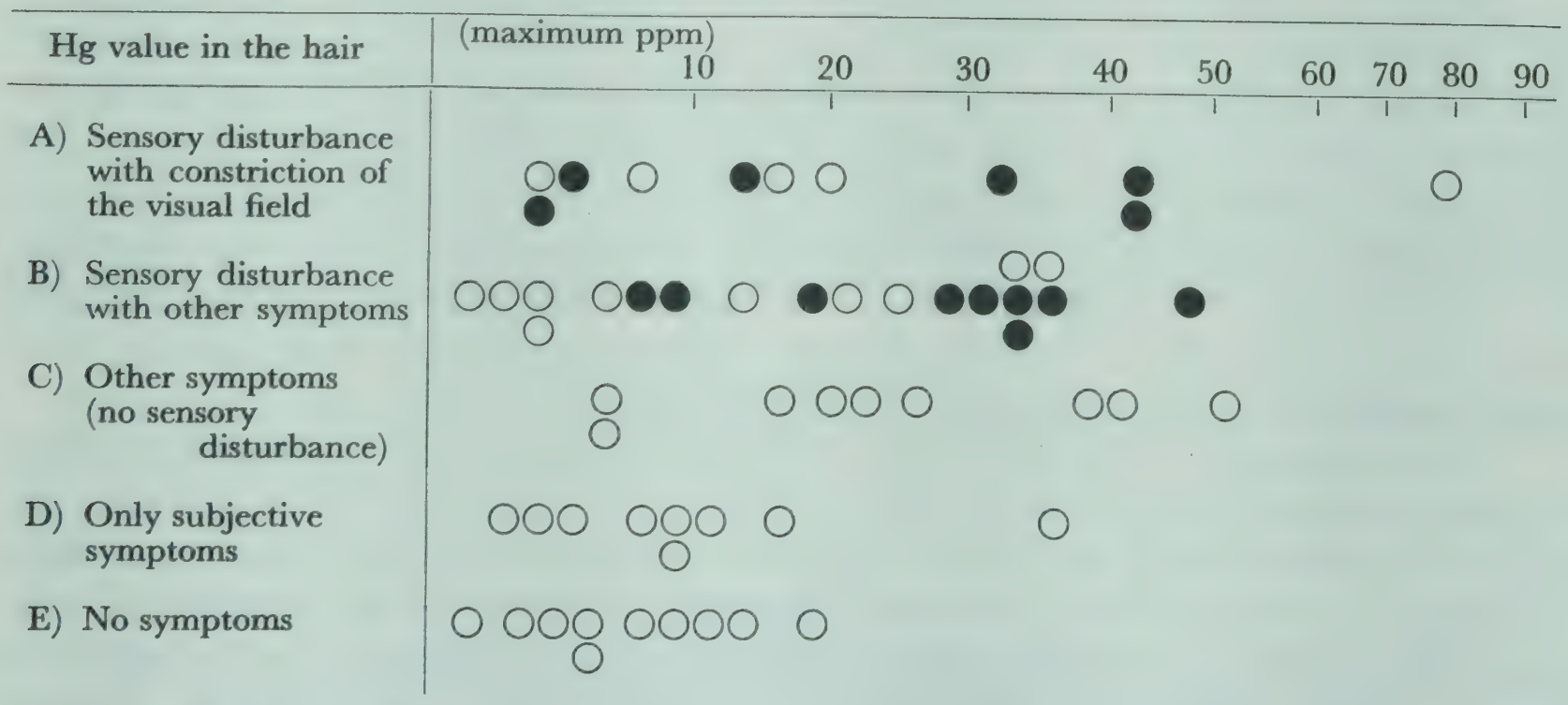

Fig. 3. Correlation between clinical symptoms and mercury value in the hair

● : Sensory disturbance of glove and stocking type

○ : Sensory disturbance of other types

Among the cases with glove and stocking type sensory disturbance (solid circles in Fig. 3), mercury content in the hair was more than 20 ppm in 10 out of 15 cases.

Discussion

Analysis of mercury in the hair has shown that inhabitants of the two Indian reserves are still being contaminated with mercury. The mercury content in the hair was high in the inhabitants who ate relatively large quantities of fishes, or who were engaged in fishing or guiding for sport fishing. The mercury value is higher in summer when fishes are more ingested.

Detection of mercury from the hair, blood or urine is often effective in diagnosing mercury poisoning. An important clue to the cause of Minamata disease in Japan was the discovery of high mercury values in the samples from patients. As was the case of Minamata disease in Japan, the contamination with mercury of the inhabitants at the reserves was continuous over a long period of time (12–15, 18). In both instances of environmental pollution in Japan and Canada, mercury values in the hair which change slowly provide a more reliable clue than such values in the urine or blood changing rapidly. Accordingly, successive analyses of mercury in the hair were effective in determining the actual degree of contamination among inhabitants, as demonstrated in this study.

Clarkson who simultaneously presented similar results on the reserves to those of the authors showed seasonal changes in, and higher values of mercury content of the hair of the inhabitants (maximum 105 ppm), for instance, a fishing guide and his family with a high mercury content in the hair and with similar seasonal changes in mercury values among family members. This led him to the belief that the mercury contamination was due to food intake (20). Clarkson also compared the mercury content of the hair with that of the blood: 30 ppm in the hair and, in contrast, about 100 ppb in the blood (20).

Now, it is very difficult to correlate the mercury content of the hair with appearance of symptoms characteristic of Minamata disease. The mercury value in the hair only serves as a cross-sectional index of contamination at a certain period. Concerning Minamata disease in Niigata, Tsubaki once assumed that 50 ppm of mercury in the hair represented a threshold of the disorder. Later it has been shown, however, that even if the pollution is apparently terminated and the mercury content in the hair diminishes, the symptoms may still appear (14, 15). The authors demonstrated that mercury levels in the hair at the time of ingestion did not necessarily coincide with severity of the clinical symptoms which appeared ten years later (17, 18).

As was pointed out by the authors, the Indian reserves in Canada did not reveal the case absolutely typical of Minamata disease (9). One reason for this was that subjects examined by the authors were actively engaged in guiding or fishing, and thus belonged to relatively healthy group. However, paraconcentric constriction of the visual fields, glove and stocking type sensory disturbance, and tremor, all of which are seen in patients of Minamata disease, were also detected at the reserves (9). Though the mercury content in the hair is of limited clinical value, its levels were higher in the cases with the symptoms than in those without them (14, 15, 18).

The mercury contamination in Canada is less in its extent than that in Minamata, and some certain differences exist in manifestations of the contamination between the two localities. In Minamata 100,000 people live in an area in size nearly equal to the two reserves in Canada. Inhabitants of Minamata ingest fish and shellfish throughout the year, and they do not have such a strong liking for alcohol (21). In Minamata the source of pollution exists in densely populated area, and many people have lived around the outlet of effluent. It is said that mercury, in amount of 600 tons, was discharged from the outlet (18). The plant was producing acetaldehyde and methylmercury discharged directly into the sea (12, 13, 18). In case of Canada, the population is sparse, the source of pollution is far from the reserves, and in winter the lakes and rivers freeze so that the intake of fish is greatly reduced. The factory produces caustic soda on a relatively smaller scale, 10 tons of mercury were discharged from there, and inorganic mercury was being discharged (2, 6).

The mechanism of methylation of inorganic mercury still remains unanswered (22), but more than 80% of mercury detected in fishes from the Wabigoon river was methylmercury (5). The fish obtained at Clay Lake was fed to cats, which experimentally induced methylmercury poisoning (5, 10).

In short, differences in the ratio of morbidity and severity of symptoms are found between the cases in Canada and Japan, but there is no essential dissimilarity in them.

It was the report of Hunter and Russell which first suggested that Minamata disease studied at that time coincided, clinically and pathologically, with those reported in Hunter's paper (23, 24). However, as the extent of polluted areas was fully exposed, it was realized that such typical and serious cases were likely to be only tips above sea level of icebergs (18).

It has become clear that atypical (incomplete) and mild cases vastly outnumber typical and severe ones. In some patients, symptoms were so mild that only sensory disturbance was observed, where diagnosis could not have been decisive unless typical cases were found among their family members, or mercury contamination was proven. In the future, mass outbreaks of serious and typical cases, such as those seen in Minamata or Niigata, may not occur.

If pollution of mercury occurs over a long period at a lower level than that in Minamata Bay, symptoms at the first stage will be those of mild poisoning, as in incomplete and atypical Minamata disease or congenital Minamata disease. Thus, such patients as were found in Canada are suspected of being affected by methymercury poisoning.

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